The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients

Clinical article

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Object. Stereoelectroencephalography (SEEG) is a methodology that permits accurate 3D in vivo electroclinical recordings of epileptiform activity. Among other general indications for invasive intracranial electroencephalography (EEG) monitoring, its advantages include access to deep cortical structures, its ability to localize the epileptogenic zone when subdural grids have failed to do so, and its utility in the context of possible multifocal seizure onsets with the need for bihemispheric explorations. In this context, the authors present a brief historical overview of the technique and report on their experience with 2 SEEG techniques (conventional Leksell frame-based stereotaxy and frameless stereotaxy under robotic guidance) for the purpose of invasively monitoring difficult-to-localize refractory focal epilepsy.

Methods. Over a period of 4 years, the authors prospectively identified 200 patients with refractory epilepsy who collectively underwent 2663 tailored SEEG electrode implantations for invasive intracranial EEG monitoring and extraoperative mapping. The first 122 patients underwent conventional Leksell frame-based SEEG electrode placement; the remaining 78 patients underwent frameless stereotaxy under robotic guidance, following acquisition of a stereotactic ROSA robotic device at the authors’ institution. Electrodes were placed according to a preimplantation hypothesis of the presumed epileptogenic zone, based on a standardized preoperative workup including video-EEG monitoring, MRI, PET, ictal SPECT, and neuropsychological assessment. Demographic features, seizure semiology, number and location of implanted SEEG electrodes, and location of the epileptogenic zone were recorded and analyzed for all patients. For patients undergoing subsequent craniotomy for resection, the type of resection and procedure-related complications were prospectively recorded. These results were analyzed and correlated with pathological diagnosis and postoperative seizure outcomes.

Results. The epileptogenic zone was confirmed by SEEG in 154 patients (77%), of which 134 (87%) underwent subsequent craniotomy for epileptogenic zone resection. Within this cohort, 90 patients had a minimum follow-up of at least 12 months; therein, 61 patients (67.8%) remained seizure free, with an average follow-up period of 2.4 years. The most common pathological diagnosis was focal cortical dysplasia Type I (55 patients, 61.1%). Per electrode, the surgical complications included wound infection (0.08%), hemorrhagic complications (0.08%), and a transient neurological deficit (0.04%) in a total of 5 patients (2.5%). One patient (0.5%) ultimately died due to intracerebral hematoma directly ensuing from SEEG electrode placement.

Conclusions. Based on these results, SEEG methodology is safe, reliable, and effective. It is associated with minimal morbidity and mortality, and serves as a practical, minimally invasive approach to extraoperative localization of the epileptogenic zone in patients with refractory epilepsy.

Key Words • stereoelectroencephalography • epilepsy • networks • stereotactic • electroencephalography • mapping

Stereoelectroencephalography (SEEG) is a methodology that permits accurate 3D in vivo electroclinical recordings of epileptiform activity.1,4,11,17,21,22,30 Among other general indications for invasive intracranial electroencephalography (EEG) monitoring, its advantages include the following: 1) its access to recording from deep cortical structures; 2) its ability to localize the epileptogenic zone when subdural grids have failed to do so; 3) its utility in the context of possible multifocal seizure onsets with the need for bihemispheric explorations; and 4) its capability in mapping the 3D aspect of epileptic networks.8,21,34 Although it is an established technique in Europe, namely in France and Italy, the application of SEEG in the US

Abbreviations used in this paper: EEG = electroencephalography; SEEG = stereoelectroencephalography.
has only recently been implemented.\(^8\) In this context, we present a prospective series of 200 patients with refractory epilepsy who underwent SEEG at the Cleveland Clinic Epilepsy Center for extraoperative mapping of the epileptogenic zone. The goals of the current study were to provide a brief historical overview, to report on the authors’ experience with the SEEG technique, to discuss its strengths and limitations, to present several recent innovations either facilitating or supplementing the technique, and to detail the authors’ opinions regarding specific clinical indications for the SEEG methodology as preferred over other methods of invasive monitoring for difficult-to-localize medically refractory focal epilepsy.

**Methods**

This study was approved by the Cleveland Clinic Institutional Review Board. All surgical procedures were part of standard patient care, and no procedures were performed solely for research purposes.

In March 2009, SEEG electrode implantation was introduced as a new procedure at the Cleveland Clinic Epilepsy Center; between March 2009 and March 2013, 200 patients with medically refractory epilepsy underwent the procedure. All patients in this group underwent preoperative evaluation including video-EEG monitoring, MRI, PET, ictal SPECT, and neuropsychological studies. Due to incongruent noninvasive data and/or the absence of a visible lesion on MRI, recommendations for long-term implantations with SEEG electrodes were made during a weekly Epilepsy Center multidisciplinary patient management conference.

Procedures pertaining to the SEEG methodology, including implantation/removal of electrodes and SEEG-guided resections, were performed by a single surgeon (J.G.M.). Of note, SEEG electrodes were placed according to a preimplantation hypothesis of the presumed epileptogenic zone incorporating the ictal onset zone and regions of early (i.e., rapid) spread of epileptic (ictal) activity.\(^14,15,29\) In addition to the general selection criteria for invasive extraoperative monitoring, additional inclusion criteria for SEEG implantation were as follows: 1) the possibility of a deep-seated location of the epileptogenic zone in areas such as the mesial structures of the temporal lobe, cingulate gyrus and other interhemispheric regions, posterior orbitofrontal areas, insula, and depths of sulci; 2) failure of a previous subdural invasive study to clearly outline the exact location of the seizure onset zone, possibly suggesting a deeply located focus; and 3) the need for bihemispheric explorations in the context of multifocal seizure onsets.\(^8,21,34\) Patients with evidence of a lesion on MRI and with concordant noninvasive data were not considered suitable candidates for SEEG and were excluded from this study.

After an anatomy- and function-based hypothesis for the epileptogenic zone was formulated from preoperative data, a tailored implantation strategy was planned with the goal of confirming or rejecting this preimplantation hypothesis. The SEEG exploration was focused to sample pathway(s) of seizure propagation within a functional network. Based on digital fusion of stereo-contrasted volumetric T1-weighted MRI, intraoperative DynaCT (Siemens AG), and 3D digital subtraction angiography, the desired targets were reached using commercially available depth electrodes (Ad-Tech, Integra) implanted using the conventional stereotactic technique through 2.5-mm drill holes. The majority of these electrodes (i.e., 2584 electrodes) were implanted in orthogonal orientation relative to the sagittal plane, with 79 additional electrodes implanted obliquely to target the superior frontal gyrus, posterior orbitofrontal cortex, superior parietal lobule, and/or insula. Within our series, the first 122 patients were prospectively implanted using a stereotactic Leksell frame-based technique that has recently been described by our group,\(^9\) unique to only a small number of centers in North America, the remaining 78 patients were prospectively implanted with the aid of a stereotactic ROSA robotic device (Medtech).

Following SEEG electrode implantation, patients were clinically monitored and electrographic recordings of all seizure events were obtained. A second patient management conference was then held for each individual, approximately 1 week after implantation, to discuss the results and implications of the SEEG study and to decide collectively on a plan for resection. Subsequent to this meeting and approximately 6 weeks after removal of the SEEG electrodes, patients underwent a standard craniotomy for tailored resection of the hypothetical epileptogenic zone. After recovery and discharge from the hospital, all patients were followed up with regular visits (6 weeks, 3 months, 6 months, 12 months, and then every year after resection) to document their seizure outcomes over time. Of note, Engel outcomes were consistently and independently assigned by the patients’ primary epileptologist at each follow-up appointment.

Data collection included demographic and clinical features, namely seizure semiology, number and location of implanted SEEG electrodes, location of the epileptogenic zone, type of resection, and procedure-related complications. These results were correlated with pathological diagnosis and postoperative seizure outcomes for those patients undergoing subsequent resection of the epileptogenic zone.

**Results**

**Patient Demographic Data**

Demographic features are summarized in Table 1. Of

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value (%)</th>
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<tbody>
<tr>
<td>sex</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>94 (47)</td>
</tr>
<tr>
<td>female</td>
<td>106 (53)</td>
</tr>
<tr>
<td>mean age in yrs</td>
<td>32</td>
</tr>
<tr>
<td>age range in yrs</td>
<td>3–69</td>
</tr>
</tbody>
</table>
note, a total of 200 patients (94 male and 106 female) with refractory epilepsy were implanted with SEEG electrodes according to a tailored preimplantation hypothesis. The mean age was 32 years (range 3–69 years). The MRI findings were considered “nonlesional” in 91 patients (45.5%), compared with 109 patients (54.5%) who exhibited MR evidence of a lesion. Of note, 58 patients (29%) had undergone prior surgical intervention for medically refractory epilepsy (Fig. 1A). Within this group, 34 patients (58.6%) had prior invasive monitoring with subdural grids and/or depth electrodes, and 31 patients (53.4%) had undergone previous attempted resection for refractory epilepsy (Fig. 1B).

Technique of SEEG Electrode Implantation

The first 122 patients prospectively underwent SEEG electrode implantation performed using a Leksell frame-based technique that has been recently described by our group.9 In prospective fashion and following the acquisition of a stereotactic ROSA device at our institution, the remaining 78 patients of this series underwent frameless SEEG implantation under direct robotic guidance. The success rate of both techniques was comparable despite the technological advances in SEEG electrode placement, with successful identification of the epileptogenic zone in 93 patients (76.2%) undergoing the Leksell frame-based technique and in 61 patients (78.2%) undergoing frameless robotic guidance for SEEG implantation. In other words, positive mapping of the epileptogenic zone was not affected by the use of either SEEG technique in our series.

SEEG and Epileptogenic Zone Localization

In total, 2663 SEEG electrodes were implanted; 60 patients (30%) underwent right-sided implantation, 56 (28%) had left-sided implantation, and 84 (42%) had bilateral SEEG electrodes implanted. Five patients (2.5%) underwent a second SEEG electrode implantation during the same admission, to place additional electrodes for improved seizure localization. The average duration of seizure monitoring following SEEG electrode implantation was 9 days, prior to subsequent removal of electrodes. Overall, SEEG successfully identified the hypothetical epileptogenic zone in 154 patients (77%) (Fig. 2), with the temporal lobe accounting for the most common location (54 patients, 35.1%). Other common epileptogenic zone

![First-time surgery](chart1.png)

![Previous surgery](chart2.png)

**Fig. 1.** Clinical details regarding previous attempted surgical interventions for 200 patients undergoing SEEG for localization of the epileptogenic zone.  
A: Pie chart showing all patients undergoing SEEG electrode implantation either with or without prior attempted surgical intervention for treatment of refractory epilepsy.  
B: Bar graph showing the spectrum of surgical procedures for those patients with prior attempted surgical intervention. DBS = deep brain stimulation; SDDE = subdural grids and/or depth electrodes; VNS = vagal nerve stimulation.
locations included the frontal lobe (28 patients, 18.2%), distinct from the parietal lobe (19 patients, 12.3%) and the orbitofrontal region (14 patients, 9.1%). In contrast, 28 patients (18.2%) were found to have multifocal seizures; 13 (8.4%) had bitemporal seizure onsets; the epileptogenic zone was unidentified in 2 (1.3%); and 3 (1.9%) had no seizures after implantation, thereby necessitating subsequent electrode removal without resection in these cases.

**Outcomes Following Resection of the Epileptogenic Zone**

Of a total of 154 patients with confirmed epileptogenic zone localization achieved using both SEEG methodologies, 134 individuals (87%) underwent subsequent craniotomy for epileptogenic zone resection, with a minimum follow-up of at least 12 months in 90 patients within this group. Within this latter cohort, the most common type of resection was lobectomy (56 patients, 62.2%), as shown in Fig. 3. Also, Fig. 4 summarizes the pathological diagnoses made subsequent to resective surgery, with the most common finding being that of focal cortical dysplasia Type I in 55 patients (61.1%). Of note, 8 patients (8.9%) were found to have normal surgical pathology in this series.

In terms of outcomes, Fig. 5 presents the surgical outcomes for 90 surgical cases with at least 12 months of follow-up (average follow-up was 2.4 years). Specifically, 61 patients (67.8%) remained free of disabling seizures, with Engel Class I outcome, compared with 29 patients (32.2%) with Engel Class II–IV outcomes. Of note, of 27 patients (30%) in whom the epileptogenic zone was localized via SEEG to the temporal lobe, 20 (74.1%) became free of disabling seizures (Engel Class I) following resective surgery. Similarly, of 18 patients (20%) in whom the epileptogenic zone was localized to the frontal lobe, 15 (83.3%) achieved Engel Class I status subsequent to resective surgery. Finally, of 29 challenging patients (32.2%) who required bilateral SEEG implantation for extensive invasive monitoring, 18 (62.1%) underwent successful resection of an identified focus and became free of disabling seizures at last follow-up.

**Postoperative Complications**

The related surgical and medical complications arising in our series of SEEG electrode implantations are summarized in Table 2. In terms of surgical complications per electrode, we report the risk of wound infection to be 0.08%, the risk of hemorrhagic complication to be

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**Figure 2.** Bar graph showing distribution of the epileptogenic zone for 200 patients in whom SEEG electrodes were implanted. F = frontal; OF = orbitofrontal; T = temporal; P = parietal; I = insular; FI = frontal and insular; FT = frontotemporal; FP = frontoparietal; TI = temporal and insular; TP = temporoparietal; TO = temporoccipital; PO = parietooccipital; M = multifocal; BT = bitemporal; U = unidentified; NS = no seizures.

**Figure 3.** Bar graph showing the number of patients undergoing various different types of resection in a cohort of 90 patients undergoing SEEG implantation for invasive epilepsy monitoring. These 90 patients had a subsequent minimum postoperative follow-up period of at least 12 months. AH = amygdalohippocampectomy.

**Figure 4.** Bar graph showing the number of patients with various pathological diagnoses following resection for epilepsy in a cohort of 90 patients undergoing SEEG implantation for invasive epilepsy monitoring. FCD = focal cortical dysplasia (I = Type I; II = Type II); HS = hippocampal sclerosis.
Stereoelectroencephalography for epileptogenic zone localization

Fig. 5. Bar graph showing postoperative seizure control outcomes for a cohort of 90 patients undergoing SEEG implantation for invasive monitoring and subsequent resective surgery. Length of follow-up was a minimum of 12 months (average follow-up of 2.4 years).

0.08\%, and the risk of transient neurological deficit to be 0.04\%. Specifically, we report a total of 5 patients (2.5\%) with surgical complications related to wound infection, bleeding, and a transient speech deficit that resolved. Of the 2 patients with hematoma related to SEEG electrode placement, one developed a subdural hematoma requiring surgical evacuation via craniotomy, but was clinically intact and unaffected postoperatively, and the other developed an expansive intracerebral hemorrhage after electrode implantation, with need for emergency craniotomy and hematoma evacuation. Due to the poor neurological status after surgery, the family requested not to pursue aggressive medical treatment, and the patient died after 48 hours. This latter case accounts for the only death (0.5\%) reported in this series. Last, medical complications were infrequent and treatable conditions in our series.

Discussion

Historical Overview

Jean Talairach was a French psychiatrist who trained and worked at the Centre Hospitalier Sainte-Anne in Paris. With a strong interest in neuroanatomy and influenced by a local neurosurgeon, Marcel David, Talairach made the monumental decision to switch from psychiatry to neurosurgery, to focus on furthering the field of stereotactic neurosurgery. His early work led to the design of a stereotactic frame (the Talairach frame), a double-grid reference system for stereotactic localization, and the development of a brain coordinate system using the anterior and posterior commissures as reference points. With these tools, Talairach published several stereotactic atlases during his career, including one on the telencephalon that ultimately became the principal reference for SEEG and lay the groundwork for this revolutionary technique. The other coinventor of the SEEG method, Jean Bancaud, was a French neurologist and electroencephalographer who initially trained at the Groupe Hospitalier de la Pitié-Salpêtrière. He subsequently transferred to the Centre Hospitalier Sainte-Anne in Paris, and it was there that Bancaud met Talairach. Influenced by advances in the fields of neurophysiology and neuropsychology, in addition to Wilder Penfield’s cerebral mapping work in Montreal, Bancaud came to appreciate the significance of clinical symptomatology (e.g., neurological deficits, seizure semiological features, and so on) in the cerebral localization of intracranial lesions or epileptic foci. Together, Bancaud and Talairach developed an operating theater dedicated to the stereotactic investigation of epileptic seizures at the Centre Hospitalier Sainte-Anne in 1959.

In 1962, they first introduced the notion of “stereoelectroencephalography,” in reference to the implantation of intracerebral multicontact electrodes placed strategically under stereotactic guidance for the purpose of intracranially recording epileptiform activity. With the aid of this technique, they formulated a comprehensive, scientific, and unique approach to epilepsy surgery based on characterizing the anatomoelectroclinical architecture of the epileptogenic zone, which they defined as a complex structure composed of a seizure-generating pacemaker region (i.e., ictal onset zone) with extensive, interconnected relay/subrelay areas responsible for subsequent early seizure propagation and the manifestation of semiological features. According to this novel concept, the hallmark of the SEEG methodology lies in its spatiotemporal analysis of pathological electrophysiological manifestations and their correlation with seizure semiology. Ultimately, Talairach and Bancaud’s innovative work in functional and stereotactic neurosurgery provided a foundation for future generations of neurosurgeons studying epilepsy with their methods. To date, SEEG is gaining in popularity, and although it has been extensively used in Europe (namely in France and Italy), it has more recently found its way to North America.

SEEG Experience at Cleveland Clinic and Comparison With the Literature

We report here on 200 patients at the Cleveland Clinic who underwent 2663 SEEG electrode implantations for the purpose of invasive intracranial EEG monitoring, in accordance with a tailored preimplantation hypothesis to investigate and characterize the epileptogenic zone. Nearly one-third of our series (58 patients, 29\%) comprised patients who had undergone prior surgical intervention.

<table>
<thead>
<tr>
<th>Nature of Complication</th>
<th>No. of Patients</th>
<th>Complication Rate per Electrode (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wound infection</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>hematoma</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>transient speech deficit</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>medical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>urinary infection</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>C. difficile gastroenteritis</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

* DVT = deep venous thrombosis; NA = not applicable; PE = pulmonary embolism.
for medically refractory epilepsy, without success; of these, almost half (31 patients, 53.4%) had undergone previous attempted resection for epilepsy and returned with postoperative seizure recurrence. In our series, SEEG confirmed the epileptogenic zone in the majority of our patients with implanted electrodes (154 patients, 77%), with a large fraction (134 patients, 87%) undergoing subsequent craniotomy for epileptogenic zone resection. Of 90 patients with a minimum follow-up of at least 12 months, 61 (67.8%) remained free of disabling seizures (i.e., Engel Class I outcome) over an average follow-up period of 2.4 years.

Our results parallel those of previous studies in the recent literature. Munari et al. (1994) reported on their experience with SEEG in 70 patients undergoing a collective total of 712 electrode implantations. Within this cohort, the epileptogenic zone was found in 60 patients (85.7%). More recently, Guenot et al. (2001) presented a series of 100 patients collectively undergoing 1118 SEEG electrode implantations for invasive EEG monitoring, with 84 patients (84%) in whom the epileptogenic zone was identified and who underwent subsequent SEEG-guided resection. In this group, SEEG confirmed the indication for resection in 14 cases (14%) that were previously disputed on the basis of the noninvasive workup. Finally, Cardinale et al. (2013) most recently presented their experience with 6496 electrodes stereotactically implanted in 482 patients with refractory epilepsy. In this series, the SEEG methodology was successfully applied in all cases (100%), with satisfactory median entry and target point localization errors (0.78 mm and 1.77 mm, respectively). Overall, the morbidity and mortality rates (< 1%) in our series are similar to previously reported series of failed epileptogenic zone lateralization. As with any invasive procedure, there are inherent limitations to the SEEG methodology. In particular, in comparison with subdural grids (or strips), it is more challenging to map the plane continuously over an eloquent region of interest by using spaced SEEG electrodes; this is particularly relevant to mapping speech or motor function. Due to the limited number of contacts located in the superficial cortex, a contiguous mapping of eloquent brain areas cannot be obtained as in the subdural method of mapping. To overcome this relative disadvantage, the functional mapping information extracted from the SEEG method is frequently complemented with other mapping strategies, either by using diffusion tensor images or by performing awake craniotomies.

Other considerations for the placement of SEEG electrodes relate to the need for sophisticated equipment, including a stereotactic frame (or robotic system as discussed below); costly disposable electrodes and skull anchor bolts; the local neurosurgeon’s experience; and finally, the steep learning curve associated with learning the technique.

Future Directions for SEEG

With the latest surge in popularity for performing invasive SEEG studies, there has been a concomitant surge in technological innovations serving either to facilitate or supplement the technique. One important advancement relates to the development of robotic stereotactic systems, such as the ROSA device (Medtech) used at our institution or Neuramate (Renishaw Inc.), which serve to expedite the transition from one trajectory to the next for the stereotactic placement of each intracerebral electrode in a smooth, systematic, and accurate manner. In addition, the stereotactic placement of 3D electrodes into specific targets or lesions (for example, periventricular nodules, hypothalamic hamartomas, and so on) not only allows for recording from these structures, but also allows for therapeutic ablative interventions. These may take the form of radiofrequency ablation or MR-guided laser-assisted ablation (Visualase, Inc.). Moreover, stereotactic mapping of functional networks has now been rendered possible by using a combination of implanted SEEG electrodes and corticocortical evoked potentials elicited to identify white matter tracts, thereby paving the way for ongoing anatomical and functional mapping of these pathways.

Finally, it is foreseeable that improvements in SEEG...
will revolutionize current research methods for collecting intracranial, spatiotemporal EEG data for subsequent physiological and neuroengineering analyses aimed at studying epileptic activity in human subjects.\textsuperscript{12,27,28,35} Additionally, we predict that the 3D implantation of SEEG electrodes into deep, strategic nodes in an epileptogenic network will significantly advance the state of future neuromodulatory strategies,\textsuperscript{13,35} with obvious implications for current stimulatory technologies, including the Neuropace device (Neuropace, Inc.), which currently relies on 2D electrodes implanted on the cortical surface.\textsuperscript{29} Improved access to the epileptogenic network with 3D electrodes implanted using SEEG methodology, when generalized to other functional networks in the brain, may also have broad ramifications for the future development of brain-machine interfaces.\textsuperscript{33} For these reasons, it is evident that the SEEG methodology will serve as an important foundation for ongoing clinical treatment and basic science research into brain networks and the spatiotemporal activity therein, in both physiological and pathological stages.

Conclusions

The SEEG methodology is associated with minimal morbidity and mortality, and serves as a practical, minimally invasive approach to extraoperative mapping of the epileptic network in patients with refractory epilepsy. Combined with future technological developments in robotics, therapeutic ablative devices, mapping of functional networks, neuromodulation, and brain-machine interfaces, SEEG is fast becoming a definitive part of the epilepsy neurosurgeon's armamentarium for investigating and treating patients with difficult-to-treat epilepsy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: González-Martínez, Serletis, Bingaman. Acquisition of data: Serletis, Bulacio. Analysis and interpretation of data: González-Martínez, Serletis, Bulacio. Drafting the article: González-Martínez, Serletis. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Serletis. Administrative/technical/material support: Serletis, Bingaman. Study supervision: González-Martínez, Serletis, Bingaman.

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