Clinical Impact of the Blood Levels of Azoles

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Symposium "Treatment of Invasive Aspergillosis: Pharmacokinetics vs. Resistance"

20th European Congress of Clinical Microbiology and Infectious Diseases, ECCMID Vienna, April 13th, 2010

BACKGROUND

- **Pharmacological principle : quantitative relationship between drug exposure and therapeutic / toxic effect**
- **Dosing of antifungal agents based on data from PK-PD experimental models and PK studies in healthy volunteers**
- **Many factors influence the pharmacokinetics (PK) of antifungal agents : high and unpredictable blood levels**
- **Azoles first-line agents for prevention and therapy of invasive aspergillosis : INCREASING DATA SET ON CLINICALLY-APPLIED TDM**

OUTLINE

***Aspergillus*-active azoles antifungals, i.e. itraconazole, voriconazole, and posaconazole :**

- **PK variability**
- **Individualized TDM-guided dosing for**
  - **Maximal efficacy**
  - **Minimal toxicity**
- **Laboratory tools for cinically efficient TDM**

VARIABILITY

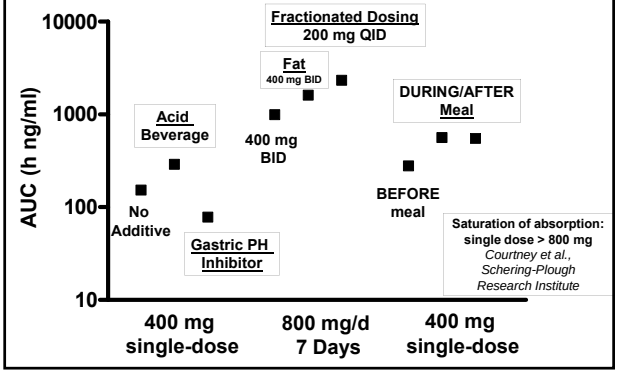
PHARMACOKINETICS OF AZOLES

Lipophilic

	Itraconazole I.V. – ORAL	Voriconazole I.V. - ORAL	Posaconazole ORAL
Food-dependent oral bioavailability	+ + Cps. POST > PRE Susp. PRE > POST	+ Cps. PRE > POST	++ Susp. POST > PRE ↓ if PPIs
Protein binding	> 99%	~ 60%	> 99%
Renal dysfunction	- (Cyclodextrin IV)	- (Cyclodextrin IV)	-
Hepatic metabolism	Oxydative (CYP), Saturable	Oxydative (CYP), Saturable	Oxydative (CYP) + Glucoronidation
Liver dysfunction	Chronic + Acute ?	Chronic + Acute ?	Chronic ? Acute ?
CYP450 genotype	?	+	?
Age < 5 years	?	+	?

Absorption of Posaconazole

Krishna et al., Antimicrobial Agents Chemother, 2009; 53: 958-66



Cytochrome P450-Mediated Drug Interactions with Azoles

Dodds Ashley et al., Clin Infect Dis, 2006; 43, S1: S28-39

	Itraconazole	Voriconazole	Posaconazole
INHIBITOR			
2C19		+++	
2C9	+	++	
3A4	+++	++	+++
Azoles modify the blood levels of co-medications			
SUBSTRATE			
2C19		+++	
2C9		+	
3A4	+++	+	
Co-medications modify the blood levels of azoles			

Cytochrome P450-Mediated Drug Interactions with Azoles

Dodds Ashley et al., Clin Infect Dis, 2006; 43, S1: S28-39

EXTENSIVE REVIEW :
8 PAGES WITH TABLES

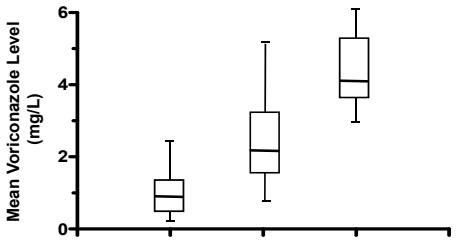
Brüggemann et al., Clin Infect Dis, 2009; 48: 1441-58

COMPLEX PROBLEM !
DO (AND CAN) PHYSICIANS CORRECTLY PRESCRIBE ?

Co-medications modify the blood levels of azoles

CYP2C19 Genotype and Voriconazole Blood Levels

Pfizer, FDA Briefing Document, 2001
http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2.htm



	Homozygous Extensive Metabolizers n=108	Heterozygous Extensive Metabolizers n=39	Homozygous Poor Metabolizers n=8
Caucasian/Blacks	70-73%	26-28%	2%
Asiatic	35-43%	43-46%	14-19%

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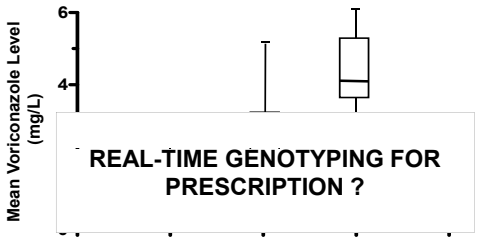

REAL-TIME GENOTYPING FOR PRESCRIPTION ?

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Caucasian/Blacks	70-73%	26-28%	2%
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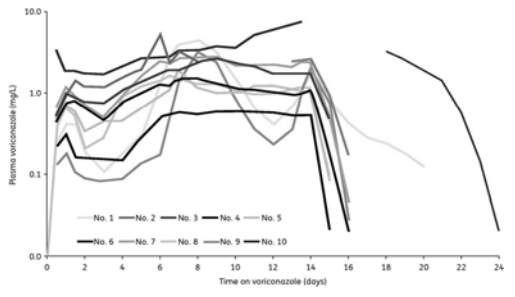
Trough Concentrations of I.V. Voriconazole Prophylaxis in Allo-HSCT Recipients

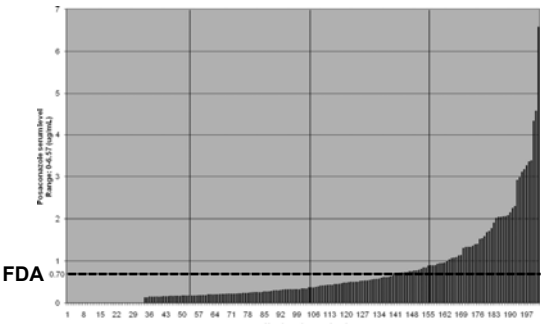
Brüggemann et al., J. Antimicrobial Chemother. 2010; 65: 107-3



The Journal of Antimicrobial Chemotherapy

Posaconazole TDM: a Reference Laboratory Experience

Thomson et al., Antimicrob Agents Chemother. 2009; 53(5): 2223-4



LARGE VARIABILITY OF AZOLES BLOOD CONCENTRATIONS

ITRACONAZOLE : MAX / MIN RATIO 200x
Poirier et al., Thérapie, 1996; 51: 163-7

VORICONAZOLE : MAX / MIN RATIO 80x
Boyd et al., Clin Infect Dis, 2004; 39: 1242-4

POSACONAZOLE : MAX / MIN RATIO 70x
Krishna et al., Antimicrobial Agents Chemother, 2007, 51: 812-8

CHILDREN < 5 YEARS

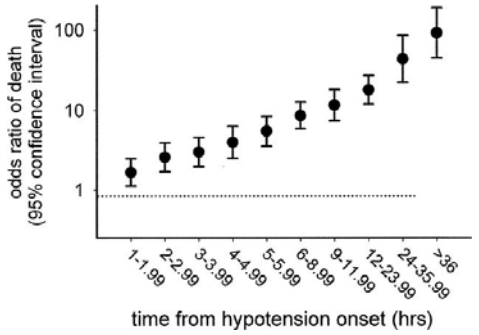
VORICONAZOLE :
> 14 mg/kg/d RECOMMENDED VS. 6-8 mg/kg/d in adults

Walsh et al., Antimicrob Agents Chemother, 2004; 48: 2166-72
Walsh, ICAAC 2007, Abs #M-620

DON'T FORGET :
THESE « SPECIAL » PATIENTS ARE DIFFERENT !

EFFICACY

Time to Appropriate Antimicrobial Therapy and Mortality in Patients with Severe Sepsis/Septic Shock
Kumar et al. Crit Care Med 2006; 34: 1589-96



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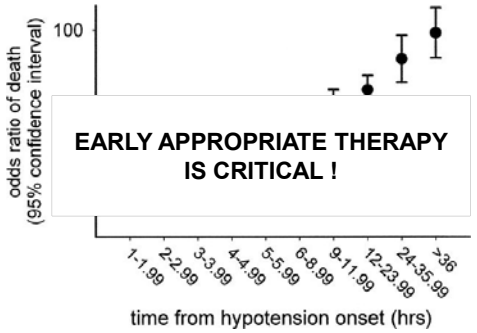


EARLY APPROPRIATE THERAPY IS CRITICAL !

EFFICACY OF AZOLE THERAPY

HOST DEFENSES

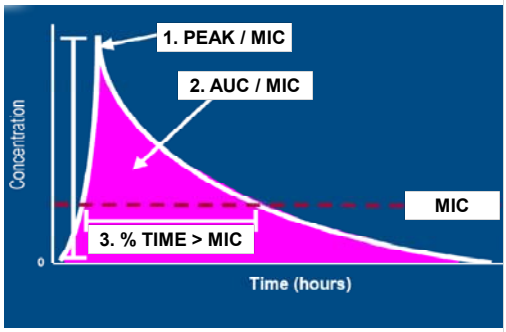
MANAGEMENT OF SITE OF INFECTION

SUCCESS

APPROPRIATE ANTIFUNGAL THERAPY

TIMING **SUSCEPTIBILITY** **DRUG DOSE**

Pharmacokinetics / Pharmacodynamics and Efficacy of Anti-Infective Therapy



Pharmacodynamics of Azoles in Experimental Invasive Aspergillosis

CORRELATION
ITRACONAZOLE PEAK LEVELS WITH TISSUE BURDEN

Berenguer et al., Antimicrobial Agents Chemother, 1994, 38: 1303-8

AUC POSACONAZOLE / MIC best predictor of survival in disseminated aspergillosis, mice (R^2 = 0.93)

Brüggemann et al., ECCMID, 2008, Abs #O21

TROUGH BLOOD CONCENTRATION :
HIGH CORRELATION WITH AUC,
MUCH EASIER FOR CLINICAL ROUTINE !
Neely et al., Clin Infect Dis, 2010; 50: 27-36
Drusano, Clin Infect Dis, 2010; 50: 37-9

MIC *Aspergillus* sp. / Moulds

	Itraconazole			Voriconazole			Posaconazole		
MIC	50%	90%	MAX.	50%	90%	MAX.	50%	90%	MAX.
Pfaller, JCM 2009, 47: 3142 *A. fumigatus*, n=637 CLSI	0.25	1	2	0.25	1	4	0.03	0.25	1
Rodriguez-Tudela AAC 2008, 52: 2468 *A. fumigatus*, n=393 EUCAST	0.25	1	2	0.5	1	2	0.06	0.25	2
Pfaller JCM 2008, 46: 2568 *Aspergillus* sp., n=771 CLSI	0.5	2	> 8	0.25	0.5	> 8	0.25	0.5	> 8
Diekema JCM 2003, 41: 3623 *Aspergillus* sp., n=373	1	2	> 8	0.5	1	> 8	0.25	1	> 8
Moulds, n= 448 NCCLS (CLSI)	1	2	> 8	0.5	1	> 8	0.25	1	> 8

Voriconazole Trough Levels and Response

Pascual et al., Clin Infect Dis, 2008; 46: 201-11

	VRC trough blood level		
	≤ 1 mg/L (n=13)	> 1 mg/L (n=39)	P value
VRC route intravenous / oral	4 (31%) / 9 (69%)	24 (61%) / 15 (39%)	0.05
Median VRC dose, mg/kg/d (range)	7 (2.5 - 9)	8 (2 - 11)	NS
Intravenous	7.5 (7 - 8)	8 (6 – 11)	NS
Oral	6 (2.5 - 9)	7 (2 - 11)	NS
Response of IFI to antifungal therapy			
Median days start of VRC to assessment, (range)	21 (10 – 120)	17.5 (10 – 180)	NS
Success	7 (54%)	34 (88%)	0.02
Complete response	5	27	
Partial response	2	7	
Persistence or progression	6 (46%)	5 (12%)	

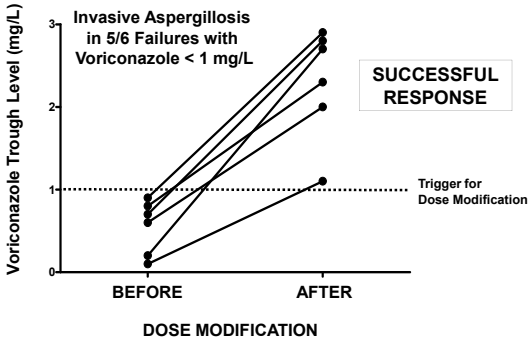
VORICONAZOLE PROPHYLAXIS, ALLO-HSCT
TROUGH BLOOD LEVEL < 2 mg/l :
↑ BREAKTHROUGH MYCOSES
(6 *Candida*, 4 zygomycetes)
Trifilio et al., BMT, 2007; 40: 451-6

ASPERGILLOSIS (24/28), ALLO-HSCT OR SOLID ORGAN TRANSPLANTS WITH MEAN BLOOD LEVEL < 2 mg/l :
↑ FAILURE
Smith et al., AAC, 2006; 50: 1570-2

VORICONAZOLE TROUGH < 2.2 mg/l in ASPERGILLOSIS:
OR FAILURE 2.7 (1.4 – 5.0)
OR DEATH 1.5 (1.1 – 2.0)
Miyakis et al., Clin Microbiol Infect, 2010 (EPub)

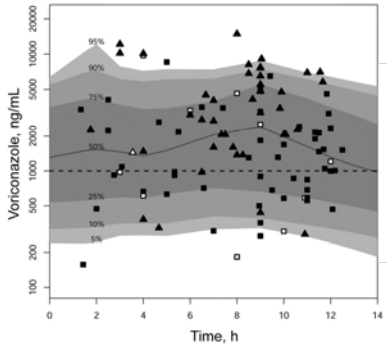
Effect of Voriconazole Dose Modification on Trough Blood Levels and Response to Therapy

Pascual et al., Clin Infect Dis, 2008; 46: 201-11



Voriconazole PK / PD in Immunocompromised Children with Invasive Mycoses

Neely et al., Clinical Infectious Diseases. 2010; 50: 27-36



VRC trough < 1 mg/L : OR death 2.6 (1.6-4.8; p=0.002)

Required dosing : 7 mg/kg b.i.d. i.v. 200 mg b.i.d. oral

Blood Levels of Posaconazole and Response to Salvage Therapy of Invasive Aspergillosis

Walsh et al., Clin Infect Dis, 2007, 44: 2-12

Quartile	No. of subjects[a]	Plasma C_{max} Mean ng/mL	Plasma C_{max} CV, %	Plasma C_{avg} Mean ng/mL	Plasma C_{avg} CV, %	No. (%) of responders
1	17	142	51	134	45	4 (24)
2	17	467	27	411	21	9 (53)
3	17	852	15	719	12	9 (53)
4	16	1480	16	1250	28	12 (75)

↑ Posaconazole Blood Levels
↑ Response to Therapy

Blood Levels in Posaconazole in Prophylaxis

FDA review of approval file for prophylaxis, 200 mg 3x/d : 44% failure with average 0.29 mg/l vs. 21% with average 0.73 mg/l

TDM with target mean level > 0.7 mg/l ?
Post-approval assessment …
Jang et al., Office Clin Pharm, FDA, Am Ass Pharm Scient Confer, 2007

Prophylaxis, 200 mg 3x/d in allo-HSCT recipients / AML-MDS pts, POSA blood conc. and BREAKTHROUGH ASPERGILLOSIS

Lower in acute GvHD / diarrhea : 5/246 (2%) breakthroughs (3 IA)
Krishna et al., Pharmacotherapy, 2007, 27: 1727-36

44% < 0.5 mg/l (diarrhea, mucositis) : 2/36 (6%) breakthrough IA
Lebeaux et al., Antimicrob Agents Chemother, 2009, 53: 5224-9

Conc. 78% < 0.5 mg/l / 94% < 0.7 mg/l : 2/18 (11%) breakthroughs
Bryant et al., ICAAC, 2009, Abs #A1-590

SAFETY

Toxicodynamics of Itraconazole

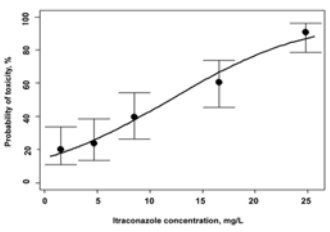
Lestner et al., Clin Infect Dis, 2009; 49: 928-30

216 patients
Chronic / allergic aspergillosis
Itraconazole cps. 100-400 mg/d
952 serum samples

Mean plasma concentration:
16 +/- 8.7 mg/l with AE vs.
7 +/- 5.9 mg/l without AE (p<0.001)

99 (46%) with adverse events:
- Fluid retention (21%):
  ↓myocardial contractility ?
- GI-tract intolerance (21%):
  nausea/vomiting > diarrhea
- Other: rash, liver, headache, tremor, sleep, mood, peripheral neuropathy

STOP in 72/99 (73%)



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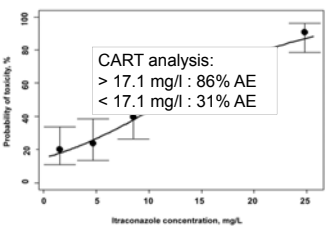
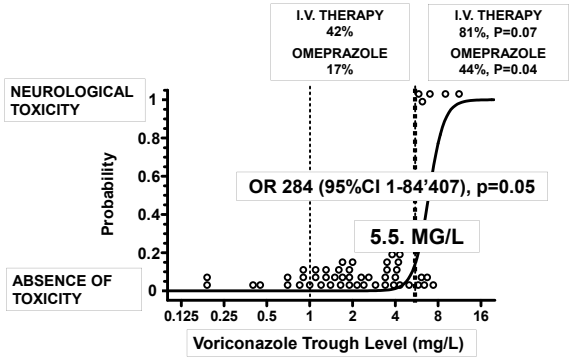


Voriconazole Trough Levels :
Logistic Regression for Neurotoxicity
Pascual et al., Clin Infect Dis, 2008; 46: 201-11



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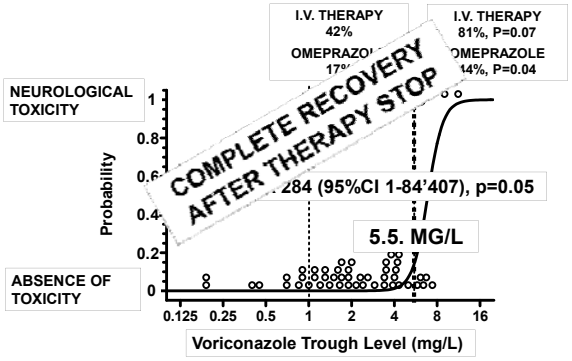


CNS SYMPTOMS
Boyd et al., Clin Infect Dis, 2004; 39: 1242-4

NEUROTOXICITY
Imhof et al., Swiss Med Weekly, 2006; 136: 739-4

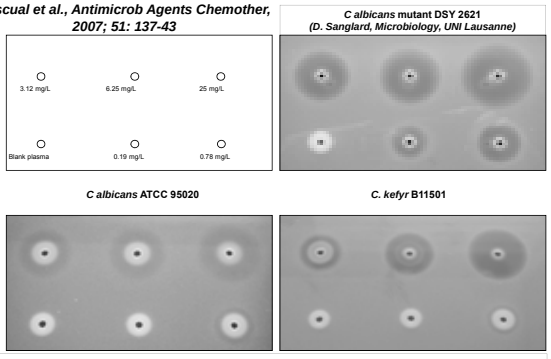
VISUAL ADVERSE EVENTS (e.g. PHOTOPSIA)
Tan et al., J Clin Pharmacol, 2006, 46: 235-43

ANALYTICAL METHODS FOR TDM OF AZOLES ANTIFUNGALS

Chromatographic methods (HPLC – LC-MS)	**Microbiologic methods (Bioassay)**
Reference methods High sensitivity / specificity Rapid analysis	Inexpensive Clinical concentration range Microbiologically active metabolites Local microbiol lab: result in 24-48 h
Expensive equipment Specialized technicians Central lab: result up to 7 days	Interferences if antifungal combination Need for cross-validation with reference chromatographic method
Itraconazole Posaconazole Voriconazole	Itraconazole Posaconazole Voriconazole

Andes et al., Antimicrob Agents Chemother, 2009; 53: 24-34

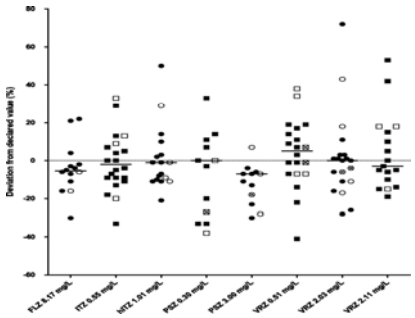
Pascual et al., Antimicrob Agents Chemother, 2007; 51: 137-43



SIMPLE + SENSITIVE + CHEAP + EXCELLENT CORRELATION WITH HPLC : FOR ANY MICROBIOLOGY LAB

International Interlaboratory Proficiency Testing Program for Measurement of Azole Antifungals Plasma Concentrations

Brüggemann et al., Antimicrobial Agents and Chemother. 2009; 53: 303-5



International Interlaboratory Proficiency Testing Program for Measurement of Azole Antifungals Plasma Concentrations

Brüggemann et al., Antimicrobial Agents and Chemother. 2009; 53: 303-5

33 European labs (73% HPLC, 18% LC-MS, 9% BIOASSAY)

ONLY 55% labs with accurate and precise results for all drugs (fluconazole, itraconazole/OH-itraconazole, voriconazole, posaconazole)

Feed-back for reassessment / improvement of techniques
2 runs/year for continuous monitoring of analytical quality

CONCLUSIONS AND PERSPECTIVES

Evidence for Azoles' TDM

- VARIABILITY of blood concentrations : multiple factors influencing drug absorption, distribution, and elimination
- Fungal pathogens with DECREASED SUSCEPTIBILITY : need for optimal adjustment of drug exposure
- TROUGH blood levels in retrospective > prospective studies :
  - 20-25% NOT in estimated therapeutic range (0.5-1 to 5-6 mg/L)
  - FAILURE if UNDERDOSING
  - TOXICITY if OVERDOSING
- Tentative Recommendations for Azoles' TDM
  Andes et al., Antimicrob Agents Chemother, 2009; 53: 24-34

High-Throughput Multiplex Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry UPLC-MS/MS Analytical Methods

Decosterd, Rochat et al., 2010 (Submitted)

Simultaneous quantification of a panel of antifungals in plasma (fluconazole, itraconazole / hydroxy-itraconazole, posaconazole, voriconazole / voriconazole-NO, anidulafungin, caspofungin) :

- Single extraction procedure; isotopic deuterated internal standards
- Single analytical run 5-10 minutes
- High sensitivity, selectivity, accuracy and precision
- Validation: internal (**FDA**), external (**EURO Interlab Program**)
- **Analytical results within 12-24h: key of clinically efficient TDM**

Future of Azoles' TDM: Consolidation of Evidence and Practicability

- Population PK +/- genotyping : individual dosing nomograms ?
- Patients' selection for TDM : all ? critically ill ? organ dysfunction ? site of infection ? MIC ? not responding / suspected toxicity ?
- Therapeutic range : prospective studies of blood concentrations associated with efficacy / toxicity before/in phase 3 (FDA ?!)
- Total or free blood concentration ? Does it reflect exposure at site of infection (e.g. lung levels might be >> plasma) ?
- Real-time interdisciplinary team (ID, pharmacologist, microbiologists) for QC, interpretation, and dosing modification
- Cost-benefit assessment: lab costs ? increased drug dosing ?

SEVERELY ILL PATIENTS WITH LIFE-THREATENING INVASIVE MYCOSES :

In Dubio, … Pro TDM

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