Clinical Pharmacogenetics Implementation Consortium (CPIC®) Guideline for *CYP2C19* and Voriconazole Therapy

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Abstract (75 word limit)

Voriconazole, a triazole antifungal agent, demonstrates wide interpatient variability in serum concentrations, due in part to variant *CYP2C19* alleles. Individuals who are CYP2C19 ultrarapid metabolizers have decreased trough voriconazole concentrations, delaying achievement of target blood concentrations; whereas, poor metabolizers have increased trough concentrations and are at increased risk of adverse drug events. We summarize evidence from the literature supporting this association and provide therapeutic recommendations for the use of voriconazole for treatment based on *CYP2C19* genotype (updates at https://cpicpgx.org/guidelines/ and www.pharmgkb.org).

Introduction

The purpose of this guideline is to provide information that allows evidence-based interpretation of clinical *CYP2C19* genotype test results in order to guide dosing of voriconazole or selection of an alternative antifungal agent for treatment that is not significantly metabolized predominantly by CYP2C19. Detailed guidelines for the use of voriconazole, as well as cost effectiveness analyses of *CYP2C19* genotyping, are beyond the scope of this document. The Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines are periodically updated at http://www.pharmgkb.org and https://cpicpgx.org/guidelines/.

Focused Literature Review

A systematic literature review focused on *CYP2C19* genotype and voriconazole use was conducted. We searched the PubMed® database (1966 to May 2016) for the following keywords: (cytochrome P450 2C19 or CYP2C19) AND (voriconazole) for the association between *CYP2C19* genotypes and metabolism of voriconazole or voriconazole-related adverse drug events or clinical outcomes. Key publications of clinical pharmacogenetic studies on voriconazole pharmacokinetics and associated clinical outcomes are reported in **Supplemental Table S1**.

Gene: *CYP2C19*

A gene summary on *CYP2C19* is available online at PharmGKB: http://www.pharmgkb.org/gene/PA124#tabview=tab3&subtab=31 (1). Like other *CYP450* superfamily members, *CYP2C19* is highly polymorphic with 35 defined variant star (*) alleles (http://www.cypalleles.ki.se/cyp2c19.htm). The wild-type *CYP2C19*1* allele encodes a normal

function CYP2C19 enzyme, and the most common no function allele is **2* (c.681G>A; rs4244285). Other *CYP2C19* alleles with decreased or no function have been identified (e.g., **3 - *8*); however, they are typically rare in the general population with the exception of *CYP2C19*3* (c.636G>A; rs4986893) in Asians. In contrast, the increased function *CYP2C19*17* allele (c.-806C>T; rs12248560) results in enhanced transcription and increased enzyme activity for some substrates. Patients with one normal/increased function allele and one decreased function allele or with two decreased function alleles are categorized as "likely intermediate metabolizers" (e.g., *CYP2C19*1/*9, *9/*9*, **9/*17*) (see supplement for more details). Allele frequencies and diplotype and phenotype frequencies calculated based on allele frequencies are provided in the CYP2C19 frequency table (2).

Genetic Test Interpretation

Each named star (*) allele is defined by the genotype of one or more specific variants, some of which are associated with a level of enzyme activity (see *CYP2C19* allele definition table (2)). **Table 1** summarizes the assignment of the likely CYP2C19 metabolizer phenotypes based on *CYP2C19* star (*) allele diplotypes, and these assignments are used to guide the *CYP2C19*-directed voriconazole treatment recommendations (**Table 2 and 3**).

Previously published CPIC guidelines for clopidogrel and tricyclic antidepressants (3, 4) define CYP2C19 ultrarapid metabolizers as individuals who carry one *CYP2C19*17* allele in combination with a normal function *CYP2C19*1* allele or who are *CYP2C19*17* homozygous. This definition was based on pharmacokinetic data that analyze *CYP2C19*17* carriers (**1/*17* and **17/*17*) from non-carriers of *CYP2C19*17* (*CYP2C19*1/*1*) separately (5, 6). This

guideline introduces the term "CYP2C19 rapid metabolizer" to define those who carry one *CYP2C19*17* allele in combination with a normal function *CYP2C19*1* allele. Statistical differences in mean pharmacokinetic parameters between *CYP2C19*1/*17* and *CYP2C19*1*/**1* has been observed, but the range of pharmacokinetic parameters often overlaps (7, 8). Whether this definition of rapid metabolizer is appropriate for all CYP2C19 substrates is unclear and may depend on the impact of other metabolic pathways involved in the metabolism of each drug (8, 9). As this distinction may be drug dependent, introducing the term "rapid metabolizer" allows for a distinctive recommendation between these phenotype groups when needed. Of note, the limited data available distinguishing rapid (**1/*17*) and ultrarapid (**17/*17*) *CYP2C19* metabolizers treated with voriconazole prompted similar recommendations for these two CYP2C19 metabolizer phenotypes in adults. However, for children, as there is insufficient evidence to distinguish a *CYP2C19*1/*17* and *CYP2C19*1/*1* pediatric patient due to large variability in trough concentrations, there are separate recommendations for CYP2C19 ultrarapid and rapid metabolizers.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental findings

Variant *CYP2C19* alleles have been associated with the development of voriconazole-associated squamous cell carcinoma; however, this study has not been adequately replicated at this time to

warrant any clinical action (10). CYP2C19 is directly involved in the metabolism of proton pump inhibitors, and variant *CYP2C19* alleles have been implicated in the development and progression of gastritis, peptic ulcer disease, and gastric carcinoma (11). In addition, no function *CYP2C19* alleles have reproducibly been associated with lower active metabolite levels of clopidogrel, decreased metabolism of metamizole, decreased platelet inhibition, and increased adverse cardiovascular event rates among clopidogrel-treated acute coronary syndrome patients undergoing percutaneous coronary intervention (4). CYP2C19 and CYP2D6 are involved in the metabolism of tricyclic antidepressants and selective serotonin reuptake inhibitors, and the available evidence supporting an association between variant alleles and antidepressant response prompted *CYP2C19* and *CYP2D6* genotype-directed CPIC guidelines for these medications (3, 8).

Drug: Voriconazole

Background

Voriconazole is a triazole antifungal agent that inhibits ergosterol synthesis by inhibiting lanosterol 14α-demethylase. It is approved for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, disseminated *Candida* infections, esophageal candidiasis, as well as infections caused by *Scedosporium apiospermum* and *Fusarium* spp. Guidelines from the Infectious Diseases Society of America (IDSA) recommend voriconazole as primary therapy for invasive aspergillosis and as an alternative therapy for candidemia (12, 13). Although voriconazole is used for prophylaxis against invasive aspergillosis in high risk patients who are neutropenic or undergoing hematopoietic stem cell transplantation, the recommendations in this guideline are focused on the use of voriconazole for treatment of

invasive fungal infections. Voriconazole is metabolized *in vitro* predominantly by CYP2C19 with contribution from CYP3A and CYP2C9 (14). This drug is also an inhibitor of CYP3A4, CYP2C19, and CYP2C9. Wide interpatient variability is observed in voriconazole concentrations, which are due to variant *CYP2C19* alleles, age, hepatic function, concomitant medications, and inflammation (phenoconversion) (14-18). Furthermore, in adults, voriconazole exhibits saturable nonlinear pharmacokinetics at greater than 3 mg/kg IV every 12 hours (19). Linear pharmacokinetics in children are observed with voriconazole at dosages between 3 to 4 mg/kg every 12 hours, which may be due to higher first-pass metabolism and systemic metabolic rates (20, 21). However, non-linear pharmacokinetics in children are observed at higher voriconazole dosages receiving 7 to 8 mg/kg every 12 hours (20, 22).

The adverse events of voriconazole include hepatotoxicity, neurotoxicity (visual hallucinations, encephalopathy, neuropathy), photopsia, skin rash, photosensitivity, visual disturbances, and periostitis with or without hyperfluorosis (23). Adverse effects that have been correlated with voriconazole concentrations include hepatotoxicity, visual disturbances, visual hallucinations, and other neurologic disorders (24-27). In addition, a decreased clinical response has been reported with low voriconazole concentrations (24, 26, 28). Due to the interpatient variability in voriconazole pharmacokinetics and to avoid the toxicity associated with elevated concentrations and therapeutic failures with low concentrations, voriconazole therapeutic drug monitoring (TDM) has been recommended.

A recent prospective, randomized, single-center study indicated that voriconazole TDM may be beneficial, as it decreased discontinuation due to adverse events and increased clinical response rate (29). A trough concentration of 1.0 to 4.0 mcg/ml has been suggested for voriconazole in treatment of most invasive mycoses caused by aspergillosis. The relationship

between voriconazole concentrations, efficacy and toxicity and the role of voriconazole TDM has been extensively reviewed elsewhere (30, 31).

Standard Dosing of Voriconazole

Voriconazole for treatment of invasive aspergillosis and other mould infections in adults is administered as an initial loading dose of 6 mg/kg IV every 12 hours for two doses followed by 4 mg/kg IV every 12 hours maintenance. Oral therapy can be used in adults at 200–300 mg every 12 h or administered orally at 3-4 mg/kg every 12 h. By comparison, the dosage in children that is necessary to achieve plasma concentrations that are similar to those attained in adults is 8 mg/kg IV or PO Q12h (22, 23, 32). Older adolescents may be dosed as adults; however, younger adolescents and those weighing less than approximately 50 kg should be dosed by body weight. Attainment of target trough concentrations is verified with TDM.

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking *CYP2C19* genotype with phenotypic variability in voriconazole pharmacokinetics (see **Supplemental Table S1**). Application of a grading system to evidence linking genotypic to phenotypic variability indicates a high quality of evidence in the majority of cases (see **Supplemental Table S1**). This body of evidence provides the basis for recommendations in **Tables 2** and **3**. The adult recommendation for *CYP2C19*17/*17* (CYP2C19 ultrarapid metabolizer) is based upon data extrapolated from individuals with *CYP2C19*1/*17* as these groups were combined in most of the studies for analyses. Evidence for an association between poor metabolizers and adverse events on voriconazole is limited to a single case report (**Supplemental Table S1**). However, strong

association between poor metabolizers and increased voriconazole concentrations has been documented. Increased voriconazole concentrations result in adverse events and this provides the basis for a recommendation for use of an alternative agent in these individuals. Additionally, cases have been reported in CYP2C19 poor metabolizers who discontinued voriconazole due to elevated and potential toxic concentrations. In the case of CYP2C19 intermediate metabolizers (e.g., *CYP2C19*1/*2, CYP2C19*1/*3*), the paucity of studies and their inconsistent findings prevented the authors of this guideline from making a recommendation for these patients.

Therapeutic Recommendation

Clinical studies have not consistently demonstrated an association between *CYP2C19* genotype and adverse reactions. However, as individual patients who are poor metabolizers may have elevated levels leading to toxicity, the use of another antifungal agent is recommended. Under circumstances where voriconazole is strongly indicated for treatment of an invasive mycosis in a patient with a poor metabolizer phenotype, administration of a lower dosage with meticulous therapeutic drug monitoring may be feasible (**Table 2 and 3**).

Knowledge of CYP2C19 ultrarapid and rapid metabolizer genotypes may prevent subtherapeutic concentrations of voriconazole that may lead to treatment failure. In such cases, an alternative antifungal agent also is recommended, especially as several case reports have documented voriconazole treatment failure in CYP2C19 ultrarapid metabolizers (see **Supplemental Table S1**). Attempting to obtain therapeutic levels in patients with ultrarapid metabolizer genotypes are often unsuccessful. Serious delays in achieving therapeutic concentrations in such patients with active invasive mycoses may result in disease progression.

There are several alternative agents that may be used instead of voriconazole for treatment of invasive mould infections. These include isavuconazole, lipid formulations of amphotericin B, and posaconazole (**Tables 2** and **3**). The antifungal triazole isavuconazole is approved for the primary treatment of invasive aspergillosis and invasive mucormycosis and is available in intravenous and oral dosage forms. As isavuconazole is a substrate of CYP3A4, variant alleles in this gene are unlikely to affect its clearance. Only limited data for isavuconazole are currently available in the pediatric population. Liposomal amphotericin B is an alternative therapy to voriconazole for the primary treatment of invasive aspergillosis. - Posaconazole is currently indicated for salvage therapy of invasive aspergillosis. The recently approved posaconazole delayed release and intravenous dosage forms achieve higher concentrations than that of the posaconazole suspension. However, intravenous posaconazole requires administration via a central line due to phlebitis with peripheral administration. Similar to voriconazole, intravenous posaconazole also contains the solubilizer sulfobutylether-beta-cyclodextrin sodium. Posaconazole is cleared largely as unchanged compound with <20% of compound being excreted as a glucuronide conjugate. Uridine 5'-diphospho-glucuronosyltransferase (UDP) glucuronidation of posaconazole is not significantly affected by genetic variation. Administration of posaconazole should still be guided by TDM.

Other considerations

Further dose adjustments of voriconazole or selection of alternative therapy may be necessary due to other clinical factors such as drug interactions, hepatic function, fungal species, TDM, comorbidities, and site of infection. Assessment of drug interactions with a patient's concomitant medications is important before initiating voriconazole. Voriconazole is a potent

CYP450 enzyme inhibitor and interacts with numerous medications including calcineurin inhibitors, sirolimus, vinca alkaloids, cyclophosphamide, and HMG-CoA reductase inhibitors (33). By comparison, CYP2C19 inhibitors such as omeprazole and cimetidine may lead to increased voriconazole concentrations. CYP3A4 inhibitors may increase voriconazole concentrations in patients who are CYP2C19 poor metabolizers (34). Furthermore, concomitant use of CYP450 enzyme inducers may lead to subtherapeutic voriconazole concentrations and clinical failure. In patients with mild to moderate hepatic impairment, a dose adjustment for voriconazole is recommended. However, selection of an alternative antifungal agent may be reasonable in patients with significant hepatic impairment due to the risk of voriconazole hepatotoxicity. In patients with renal failure, the solubilizer of intravenous voriconazole (sulfobutylether-beta-cyclodextrin sodium) may accumulate (35). Although the manufacturer suggests using oral voriconazole in patients with CrCl < 50 ml/min unless the benefits outweigh the risk, there appears to be no deleterious effect of the sulfobutylether-beta-cyclodextrin in this patient population receiving the parenteral formulation. The availability and turnaround time of voriconazole concentrations at an institution may affect the ability to perform voriconazole TDM. Finally, comorbid conditions such as obesity may require using an adjusted body weight instead of total body weight when using weight based dosing of voriconazole (36).

Genetic variation in *CYP3A4*, *CYP3A5* and *CYP2C9* appears not to significantly affect the pharmacokinetics of voriconazole (16, 17, 37-40). In an analysis of the placebo groups of two drug interaction studies in healthy volunteers, *CYP3A5* variants did not affect the pharmacokinetics of voriconazole (17). The lack of association of *CYP3A5* and voriconazole pharmacokinetics was also observed in a single and multiple dose voriconazole study in healthy volunteers (16). Furthermore, the pharmacokinetic parameters of voriconazole in a CYP2C19

normal metabolizer patient with a *CYP2C9*2/*2* genotype were similar when compared to patients with a *CYP2C9*1/*1* genotype (38).

Implementation of this guideline. The guideline supplement contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* sections of supplement.).

Potential Benefits and Risks for the Patient

Voriconazole dosing is routinely directed by therapeutic drug monitoring. However, for patients with available *CYP2C19* genotyping results, subtherapeutic and supra-therapeutic voriconazole concentrations could be avoided by choosing alternative agents in ultrarapid/rapid metabolizers and poor metabolizers, respectively. Although *CYP2C19* genotyping is considered reliable when performed in qualified clinical laboratories, genotyping and/or human error is always a rare possibility. Prospectively collected data from studies seeking to establish and validate dosages in poor metabolizers are needed in order to provide additional options to clinicians caring for these patients.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

CYP2C19 genotyping cannot replace therapeutic drug monitoring, as other factors (i.e. drug interactions, hepatic function, renal function, species, site of infection, and comorbidities) also influence the use of voriconazole. Rare *CYP2C19* variants are typically not included in common

genotyping tests and patients are therefore assigned the "wild-type" (*CYP2C19**1) allele by default. Thus, an assigned “wild-type” allele may in rare cases harbor a no, decreased or increased function variant. An individual’s predicted CYP2C19 metabolizer status may also depend on other factors including epigenetic phenomena, diet, co-morbidities, or co-medications (32).

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

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Table 1. Assignment of Likely CYP2C19 Phenotypes Based on Genotypes

Likely phenotype	**Genotypes**[b]	**Examples of *CYP2C19* diplotypes**
CYP2C19 Ultrarapid Metabolizer (~2-5% of patients)[a]	An individual carrying two increased function alleles	**17/*17*
CYP2C19 Rapid Metabolizer (~2-30% of patients) [a]	An individual carrying one normal function allele and one increased function allele	**1/*17*
CYP2C19 Normal Metabolizer[c] (~35-50% of patients) [a]	An individual carrying two normal function alleles	**1/*1*
CYP2C19 Intermediate Metabolizer (~18-45% of patients) [a]	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	**1/*2, *1/*3, *2/*17*[d]

CYP2C19 Poor Metabolizer (~2-15% of patients) [a]	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

[a]See the CYP2C19 frequency table (2) for race specific allele and phenotype frequencies.

[b]Assignment of allele function can be found on PharmGKB (CYP2C19 allele definition table; (2)) and citations for allele function can be on PharmGKB (CYP2C19 allele functionality references; (2)).

[c]Based on the CPIC term standardization project (reference in press), the term "Normal Metabolizer" will be used instead of the term "Extensive Metabolizer" in all new and updated CPIC guidelines.

[d]The predicted metabolizer phenotype for the**2/*17* genotypes is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP2C19*2* (5). See **Supplemental Materials** for a more comprehensive list of predicted metabolizer phenotypes.

Table 2. Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for adult patients

CYP2C19 **phenotype**	**Implications for voriconazole pharmacologic measures**	**Therapeutic recommendations**	**Classification of Recommendations**[a]
CYP2C19 Ultrarapid Metabolizer (**17/*17*)	In patients for whom an ultrarapid metabolizer genotype (**17/*17*) is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing.	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	Moderate[c]
CYP2C19 Rapid Metabolizer (**1/*17*)	In patients for whom a rapid metabolizer genotype *(*1/*17*) is identified, the probability of attainment of therapeutic	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of	Moderate

	concentrations is modest with standard dosing.	voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[b]	
CYP2C19 Normal Metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing.[b]	Strong
CYP2C19 Intermediate Metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared to normal metabolizers.	Initiate therapy with recommended standard of care dosing.[b]	Moderate
CYP2C19 Poor Metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events.	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents	Moderate

		include isavuconazole, liposomal amphotericin B, and posaconazole.[b] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	

[a]Rating scheme is described in Supplementary Data online.

[b]Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, TDM, and comorbidities.

[c]Recommendations based upon data extrapolated from patients with *CYP2C19*1/*17* genotype

Table 3. Dosing recommendations for voriconazole treatment based on CYP2C19 phenotype for pediatric patients (children and adolescents <18 years old)

CYP2C19 **phenotype**	**Implications for voriconazole pharmacologic measures**	**Therapeutic recommendations**	**Classification of Recommendations**[a]
CYP2C19 Ultrarapid Metabolizer (**17/*17*)	In patients for whom an ultrarapid metabolizer genotype (**17/*17*) is identified, the probability of attainment of therapeutic concentrations is small.	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include liposomal amphotericin B, and posaconazole.[b,c]	Moderate
Rapid Metabolizer (**1/*17*)	In patients for whom a rapid metabolizer genotype (**1/*17*) is identified, the probability of	Initiate therapy with recommended standard of care dosing.[b] Use	Moderate

	attainment of therapeutic concentrations is variable.	therapeutic drug monitoring to titrate dose to therapeutic trough concentrations.[c,d]	
CYP2C19 Normal Metabolizer	Normal voriconazole metabolism	Initiate therapy with recommended standard of care dosing.[b]	Strong
CYP2C19 Intermediate Metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared to normal metabolizers.	Initiate therapy with recommended standard of care dosing.[b]	Moderate
CYP2C19 Poor Metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events.	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include liposomal	Moderate[e]

		amphotericin B and posaconazole.[b, e] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	

[a]Rating scheme is described in Supplementary Data online.

[b]Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, TDM, and comorbidities.

[c]Achieving voriconazole therapeutic concentrations in the pediatric population with ultrarapid and rapid metabolizer phenotypes in a timely manner is difficult. As critical time may be lost in achieving therapeutic concentrations, an alternative antifungal agent is recommended in order that the child receives effective antifungal therapy as soon as possible.

[d]Meticulous therapeutic drug monitoring is critical for rapid metabolizers. There is insufficient evidence to distinguish a *CYP2C19*1/*17* and **1/*1* pediatric patient due to large variability in trough concentrations.

[e]Recommendation based upon data extrapolated from adults.