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1 **Can we predict the influence of inflammation on voriconazole exposure? An**

2 **overview**

3 Running title:

4 Inflammation's impact on voriconazole exposure

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32 **Synopsis**

33 Voriconazole is a triazole antifungal indicated for invasive fungal infections that exhibits a high
34 degree of inter-individual and intra-individual pharmacokinetic variability. Voriconazole
35 pharmacokinetics is non-linear, making dosage adjustments more difficult. Therapeutic drug
36 monitoring is recommended by measurement of minimum plasma concentrations. Several
37 factors are responsible for the high pharmacokinetic variability of voriconazole: age, feeding
38 (which decreases absorption), liver function, genetic polymorphism of the *CYP2C19* gene, drug
39 interactions, and inflammation. Invasive fungal infections are indeed very frequently
40 associated with inflammation, which engenders a risk of voriconazole overexposure. Many
41 studies have reviewed this topic in both the adult and pediatric populations, but few studies
42 have focused on the specific point of the prediction, to evaluate the influence of inflammation
43 on voriconazole pharmacokinetics. Predicting the impact of inflammation on voriconazole
44 pharmacokinetics could help optimize antifungal therapy and improve patient management.
45 This review summarizes the existing data on the influence of inflammation on voriconazole
46 pharmacokinetics in adult populations. We also evaluate the role of C-reactive protein, the
47 impact of inflammation on patient metabolic phenotypes, and the tools that can be used to
48 predict the effect of inflammation on voriconazole pharmacokinetics.

49 **INTRODUCTION**

50 Voriconazole is a triazole antifungal agent indicated for invasive fungal infections (IFIs). The
51 main indication of voriconazole is invasive aspergillosis, a life-threatening and dreaded disease
52 that occurs in high-risk patients, such as patients with hematological malignancies, solid organ
53 transplantation, or patients in intensive care units with severe immunosuppression due to
54 immunosuppressors or viral-induced acute respiratory distress syndrome. Voriconazole
55 exhibits a high degree of inter-individual and intra-individual pharmacokinetic variability.
56 Voriconazole pharmacokinetics is non-linear, which leads to more difficult dosage
57 adjustments.¹ Therapeutic drug monitoring is recommended by measurement of minimum
58 plasma concentrations (C_{min}), with a therapeutic target range between 1 to 5.5 mg/L for
59 prophylactic and curative treatment, and 2 to 5.5 mg/L for optimal curative treatment in
60 severe and complex infections.^{2,3-5} Several factors are responsible for voriconazole's high
61 degree of pharmacokinetic variability: food consumption (which affects absorption), liver
62 function, genetic polymorphism of the *CYP2C19* gene, drug interactions, and inflammation.⁶
63 The *CYP2C19* gene is highly polymorphic: the *CYP2C19**2 or *3 alleles are associated with
64 enzymatic loss-of-function, which results in an intermediate or poor metabolizer phenotype
65 leading to an increase in voriconazole exposure. The *CYP2C19**17 allele conducts to a rapid or
66 ultrarapid metabolizer phenotype and leads to a decrease in voriconazole exposure. There is
67 limited evidence for an association between variants within the *CYP3A4* gene and its impact
68 on voriconazole pharmacokinetics apart from Gautier-Veyret and He's studies.^{7,8}
69 Inflammation can affect voriconazole pharmacokinetics and may induce a risk of voriconazole
70 overexposure.⁹ Several studies have reviewed this topic in adult and pediatric populations.¹⁰
71 The C-reactive protein (CRP) level is an interesting marker of inflammation that is readily
72 available in clinical practice, and several authors have attempted to predict its influence on

73 voriconazole C_{min} . In addition, another predictive approach is evaluation of the hepatic
74 metabolic capacity by the measurement of voriconazole N-oxide C_{min} , which is the main
75 metabolite of voriconazole. Voriconazole is intensively metabolized by cytochrome P450 (CYP)
76 iso-enzymes, with only 2% excreted unchanged in urine. The main circulating metabolite,
77 voriconazole N-oxide, accounts for 72% of the radiolabeled metabolites found in human
78 plasma.¹¹ CYP2C19 is the primary enzyme responsible for the metabolism of voriconazole into
79 voriconazole N-oxide. CYP3A4, CYP2C9 and members of the flavin containing monooxygenase
80 family also contribute to the metabolism of voriconazole.¹² Measurement of both
81 voriconazole and voriconazole N-oxide C_{min} allows for calculation of the metabolic ratio (MR)
82 ($[\text{voriconazole N-oxide } C_{min}]/[\text{voriconazole } C_{min}]$) and constitutes a viable phenotyping
83 approach.¹³ This ratio is theoretically decreased during inflammation episodes. Predicting the
84 impact of inflammation on this ratio and then on voriconazole pharmacokinetics could help
85 optimize antifungal therapy. Therefore, it seems relevant to summarize the studies that have
86 sought to predict the influence of inflammation on voriconazole pharmacokinetics. Invasive
87 fungal infections are indeed very frequently associated with inflammation, which contributes
88 to voriconazole C_{min} variability and complicates patient management. This review summarizes
89 the existing data on the influence of inflammation on voriconazole pharmacokinetics, its
90 impact on patient metabolic phenotypes, and the role of CRP. Moreover we present and
91 discuss three types of tools that can be used to predict the effect of inflammation on
92 voriconazole pharmacokinetics: (i) formulas developed for the prediction of the influence of
93 CRP on voriconazole C_{min} , (ii) a phenotyping approach involving calculation of a MR, and (iii)
94 population pharmacokinetics models integrating CRP as a covariate. The final aim is to
95 optimize voriconazole dosing to improve patient care.

97 **METHODOLOGY**

98 A systematic literature search was performed using the PubMed® database with the following
99 keywords: “voriconazole” AND “inflammation”, AND “concentration” OR “level” OR
100 “pharmacokinetics”. Twenty studies were identified with the aforementioned keywords. The
101 search was limited to English-language articles, studies conducted in adult subjects, and
102 publication dates between 2003 and 2023. The abstracts of these articles were read, and
103 relevant articles were selected for this review. Articles concerning pediatric populations were
104 excluded, as were articles with paid access. The analysis of these articles resulted in the
105 selection of 15 articles of interest linked to the subject of the present review. However, few
106 articles directly address this topic. Formulas developed for prediction of the influence of CRP
107 on voriconazole C_{min} have been taken from the literature and tested using data from the
108 Boglione-Kerrien study.¹⁴

109 **RESULTS**

110 **Impact of inflammation on voriconazole C_{min} and the role of CRP**

111 The influence of inflammation on voriconazole metabolism is now well-established.
112 Inflammatory cytokines cause modulation of the activity of drug-metabolizing enzymes and
113 transporters (DMET). The concentrations of specific proteins, such as CRP, increase during
114 inflammatory episodes due to the stimulation of hepatocytes by interleukin (IL)-6 cytokines.
115 Inflammation plays an inhibitory role on DMETs, with a significant impact on drugs with a
116 narrow therapeutic index, such as voriconazole.¹⁵ There is a decrease in the metabolic activity
117 of CYP2C19 and CYP3A after an acute inflammatory state (e.g., during surgery), which has
118 been assessed by intake of a phenotyping cocktail containing several drugs called “the Geneva
119 cocktail” in the study by Lenoir *et al.*¹⁶

120 Because of its wide availability, CRP is a useful marker for the evaluation of inflammatory
121 status, particularly during IFIs. In a study conducted in hematological patients exhibiting
122 invasive fungal infections, CRP was shown to be increased during inflammation: CRP was
123 measured with a median equal to 108 mg/L on Day 0 (range 5–326), and CRP >100 mg/L in
124 72% of cases between D0 and D12 of the IFI diagnosis.¹⁷ Gautier-Veyret *et al.* have
125 demonstrated that CRP > 96 mg/L leads to an increased risk of voriconazole overexposure and
126 thus represents a useful predictive marker.¹⁸ The intensity of inflammation needs to be taken
127 into account, and a high inflammatory response highlighted by high CRP concentrations
128 strongly impacts voriconazole pharmacokinetics.¹⁹ Indeed, more severe inflammation has a
129 greater impact on voriconazole C_{min} and the MR.²⁰ Concomitant measurement of CRP in
130 patients treated with voriconazole as proposed by Le Daré *et al.*, may help predict voriconazole
131 overexposure episodes.²¹ An observational study of hematological patients showed the
132 predictive value of a combination of biomarkers associating high CRP (> 120 mg/L) with low
133 concentrations of procalcitonin or presepsin for IFIs.²² In a prospective study that included 61
134 patients, the impact of the CRP level on voriconazole C_{min} was evaluated, and an extract of 12
135 profiles of inflammatory patients is presented in Figure 1. The voriconazole C_{min} changes
136 concomitantly with the CRP concentration. However, there is significant variability in the
137 inflammatory profiles encountered (i.e., the duration of inflammation, the time of
138 inflammation in relation to the treatment and, therefore, to the infection).¹⁴

139 The relevance of measuring another marker of inflammation with a better predictive value
140 was also highlighted within the literature. Rather than CRP, IL-6 can be measured because its
141 effect is more directly related to the inflammatory process, and it may provide more precise
142 information. Vreugdenhil *et al.* found a significant but moderate correlation between IL-6 and
143 voriconazole C_{min} . Thus, taking IL-6 into account as an inflammatory marker does not appear

144 to be more informative than using CRP.²³ A positive correlation has also been shown between
145 IL-18 or transforming growth factor (TGF)- β 1 and voriconazole C_{min} , but the authors did not
146 indicate whether practical and predictive use could be considered.²⁴

147 The significant variability of the inflammatory profile between patients shows that prediction
148 can, therefore, be difficult, but CRP measurement is nevertheless useful.

149 **Formulas to predict the influence of CRP on voriconazole C_{min}**

150 Several authors have sought to predict the influence of CRP on voriconazole C_{min} and the
151 MR.^{9,25–28} Of these studies, only one was prospectively conducted.²⁶ In Table 1, the different
152 formulas used in the literature to predict the influence of CRP on voriconazole C_{min} are
153 compared. To assess the relevance of these formulas, 15 inflammatory patients from the
154 Boglione-Kerrien *et al.* study were tested. Considering a maximum bias of 20% between the
155 concentrations predicted with the formulas and the observed value of the concentrations that
156 were measured (maximum measurement bias based on bioanalytical guidelines used by
157 pharmacology learning societies), no formula appears satisfactory, since a bias greater than
158 20% was obtained in approximately half of the patients. A tendency to overestimate the
159 voriconazole C_{min} was observed for certain predicted concentrations. Therefore, using this
160 small sample of external data, no prediction formula based on CRP was appropriate for
161 voriconazole C_{min} prediction.

162 **Inflammation and metabolic phenoconversion**

163 During acute inflammation episodes, voriconazole clearance by cytochromes is reduced by a
164 phenomenon called metabolic phenoconversion. The phenotype, which is mainly determined
165 by the patient's genotype but also influenced by other factors, is modified by the inflammatory
166 process. Metabolic capacity is transiently inhibited during the inflammatory process, and

167 irrespective of the patient's genotype, the patient's phenotype can then switch to a poor
168 metabolizer phenotype. The impact is significant in rapidly metabolizing patients because, in
169 this case, the profile determined by genotyping is entirely masked by the inflammation:
170 inflammatory cytokines cause a decrease in CYP450 activity leading to an increase in
171 voriconazole C_{min} .¹⁵ Although changes in CRP do not allow accurate prediction of voriconazole
172 C_{min} changes during an inflammatory episode, its measurement can be informative regarding
173 the risk of phenoconversion.¹⁵

174 Patient management is, therefore, difficult in this context. It should also be noted that
175 approximately 20% of the Caucasian population are rapid voriconazole metabolizers.²⁹ Some
176 centers undertake *CYP2C19* and *CYP3A* genotyping to determine a genetic score, but this has
177 highlighted the lack of prediction of voriconazole C_{min} in inflammatory patients.³⁰ The
178 genotype impacts the voriconazole C_{min} and the MR only in cases with mild to moderate
179 inflammation (CRP < 40 mg/L) according to Aiuchi *et al.* Thus, when the CRP level is > 40 mg/L,
180 *CYP2C19* polymorphisms are not an independent factor influencing voriconazole C_{min} and the
181 MR.³¹ The determination of genetic scores should be combined with inflammation to improve
182 prediction, as inflammation is an important parameter to be taken into account.²⁵
183 Physiologically based Pharmacokinetics (PBPK) models also use this approach, which
184 combines *CYP2C19* and *CYP3A4* genotypes and inflammation by measuring CRP.³² The
185 usefulness of genotyping downstream of infection in order to optimize patient care remains
186 to be demonstrated, particularly in cases of phenoconversion. It would be interesting to
187 obtain continuous CRP monitoring over a period of several days in order to understand the
188 dynamics of the phenomenon and to cover the entire inflammatory process from its beginning
189 to its decrease. In addition, CRP measurement is immediately available to the clinician,
190 whereas genotyping is not.

191 Figure 2 illustrates the case of a metabolic phenoconversion in a rapid-metabolizer patient
192 during an inflammatory episode.

193 **The use of phenotyping as a prediction tool: calculation of the MR**

194 The MR reflects the change in the inflammatory status. It is determined according to the
195 following formula: $MR = \frac{\text{voriconazole N-oxide } C_{\min}}{\text{voriconazole } C_{\min}}$. The higher the CRP,
196 the lower the MR, which results in reduced metabolic capacity and increased voriconazole
197 C_{\min} .³³ MR thresholds of 0.48 and 1.15 were determined based on receiver operating
198 characteristic (ROC) curve analysis in the Boglione-Kerrien *et al.* study, in which MR values
199 > 1.15 and < 0.48 were determined to be the best predictors for having a voriconazole C_{\min}
200 lower than 2 mg/L and above 5.5 mg/L, respectively, at the next visit. Sixty-eight percent of
201 observations with a low MR (< 0.48) had a CRP > 96 mg/L, compared to 45% for an MR
202 between 0.48 and 1.15 and 10% for an MR greater than 1.15. There was a 7.35-fold increased
203 risk of the MR being < 0.48 when the CRP was greater than 96 mg/L, which suggests decreased
204 metabolism with inflammation, with a median MR equal to 1. A low MR may then indicate a
205 risk of accumulation of voriconazole and an increased risk of voriconazole overexposure.¹⁴ The
206 voriconazole N-oxide concentration is generally not determined routinely, but its
207 measurement and the calculation of the MR could provide additional information regarding
208 patient metabolic capacity. The quantification of both voriconazole and the main metabolite
209 voriconazole N-oxide by a multiplex method allows determination of the MR.^{34,35} According
210 to Veringa and colleagues, this can improve patient care.²⁶ The suggested MR threshold of
211 0.48 could be an alert for the pharmacologist and may help them assess the patient's
212 metabolic capacity, the impact of inflammation, and ultimately personalize and optimize the
213 patient's dosage and follow-up. In a retrospective study conducted by Encalada *et al.*, an

214 association was shown between CRP and MR in the case of severe inflammation with CRP
215 > 100 mg/L measured on the same day as the voriconazole C_{min} .⁹ Niioka *et al.* highlighted the
216 fact that CYP2C19 activity can be assessed by measuring the MR, but that voriconazole C_{min}
217 prediction is improved by taking into account CRP, age, and the route of administration, in
218 addition to the patient's genotype.³⁶

219 **Population pharmacokinetic model – Model-informed precision dosing**

220 The use of a population pharmacokinetic model integrating an inflammation marker such as
221 CRP as a covariate, appears to be a useful tool for implementation and evaluation in real life,
222 allowing voriconazole C_{min} prediction according to the level of inflammation. Van den Born *et*
223 *al.* integrated CRP into a one-compartment model with non-linear elimination, based on 1060
224 voriconazole blood sample measurements from 54 patients. Several covariates were tested,
225 including body weight and liver enzymes (alanine aminotransferase, aspartate
226 aminotransferase, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase), but only
227 CRP improved the model. An exponential factor of 0.0048 on voriconazole clearance was
228 found, which means that the metabolic rate decreased by 50% for each 150 mg/L increase in
229 CRP. The authors specified that future research is necessary to improve the prediction of
230 voriconazole concentrations and allow a better estimation of pharmacokinetic parameters. In
231 addition, this model should be evaluated with external data to assess the performance of its
232 predictive capacity.³⁷ Furthermore, the study by Jiang *et al.* integrated CRP into a population
233 pharmacokinetic model, albeit with a more limited number of blood samples used for the
234 construction of the model (233 blood samples from 69 patients with talaromycosis endemic
235 fungal infection).³⁸

236

237 **CONCLUSION**

238 The impact of inflammation on voriconazole exposure is substantial, but prediction of the
239 change in voriconazole C_{min} in an inflammatory context remains difficult, with high inter- and
240 intra-individual variability. To date, there are still limited studies on the impact of
241 inflammation on voriconazole C_{min} . Moreover, the dynamic of the inhibitory effect of
242 inflammation on voriconazole metabolism is still to decipher. Thus, it is still challenging to
243 offer a comprehensive algorithm to guide voriconazole drug adjustment in the case of
244 inflammation. As the majority of studies have been conducted in adults, this review focused
245 only on adult patients, and no therapeutic recommendations for children can be inferred from
246 the available data. However, CRP is a widely-used, easy-to-obtain, biological parameter, and
247 its monitoring during fungal infections may help optimize voriconazole C_{min} . Indeed, CRP
248 monitoring, as a reflection of inflammatory status influencing voriconazole pharmacokinetics,
249 appears to be an essential tool in the management of patients treated with voriconazole for
250 invasive fungal infections, in addition to therapeutic drug monitoring. A CRP threshold close
251 to 100 mg/L could constitute an alert threshold for clinicians and represent an aid for
252 pharmacologists in proposing dosage adjustments. This would allow further improvement and
253 personalization of treatment. MR determination by measuring the main metabolite
254 voriconazole N-oxide concentration is also a promising tool, and this could be implemented
255 gradually in pharmacology laboratories. Ideally, CRP and MR should be included as new
256 markers of variability in model-informed precision dosing approaches to optimize
257 voriconazole C_{min} prediction and personalize voriconazole treatment. Finally, further studies
258 should focus on evaluating the added value of a CRP-driven approach on the actual TDM of
259 voriconazole.

260

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271 studies. CBK and FL performed the analysis of studies and wrote the manuscript. JPG, MCV,
272 and EB provided final approval of the manuscript in its submitted form. All authors revised the
273 manuscript for important intellectual content and approved the manuscript in its submitted
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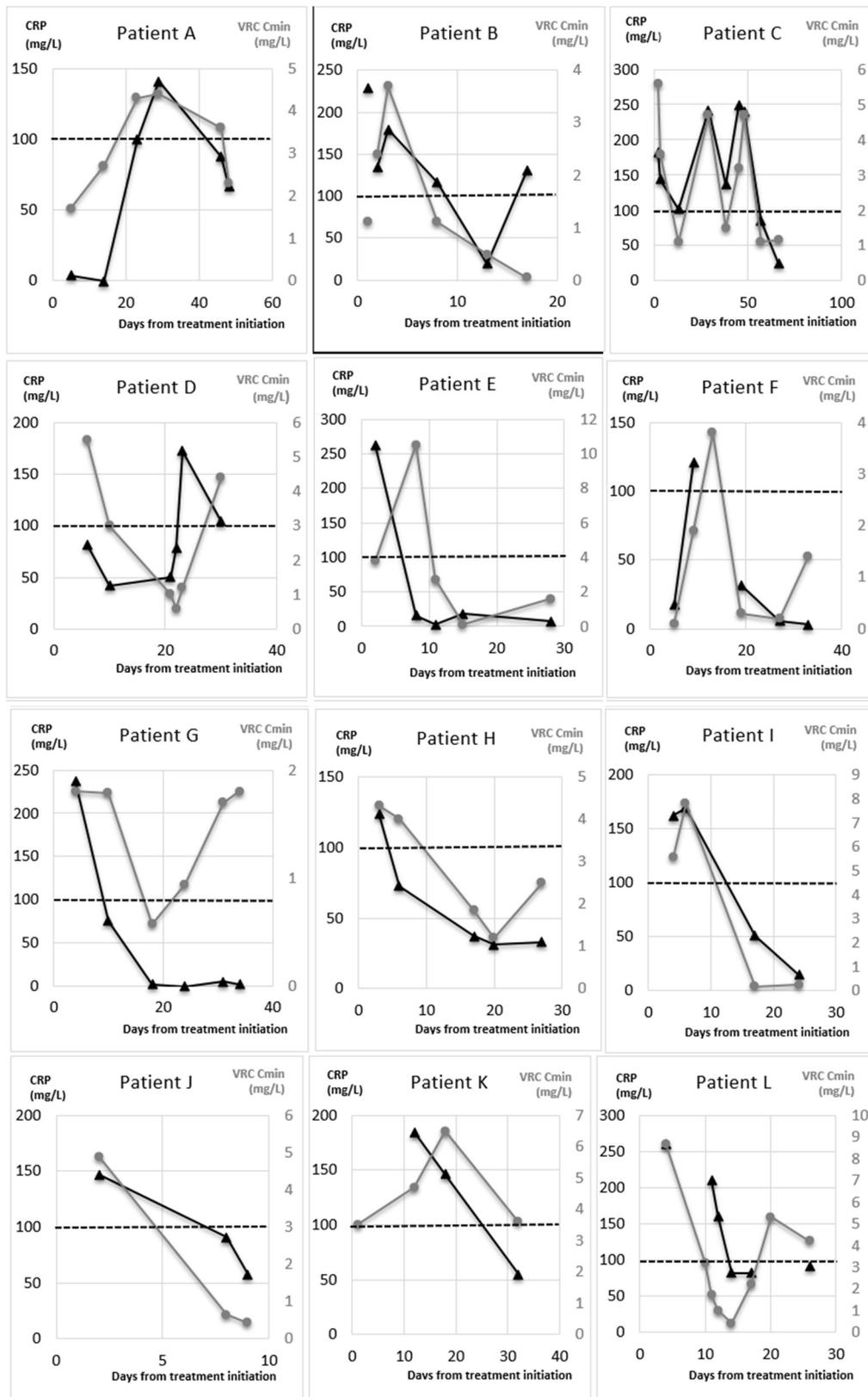
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FIGURES

Figure 1. CRP and voriconazole C_{min} changes in inflammatory patients
(from Boglione-Kerrien *et al.*¹⁴)



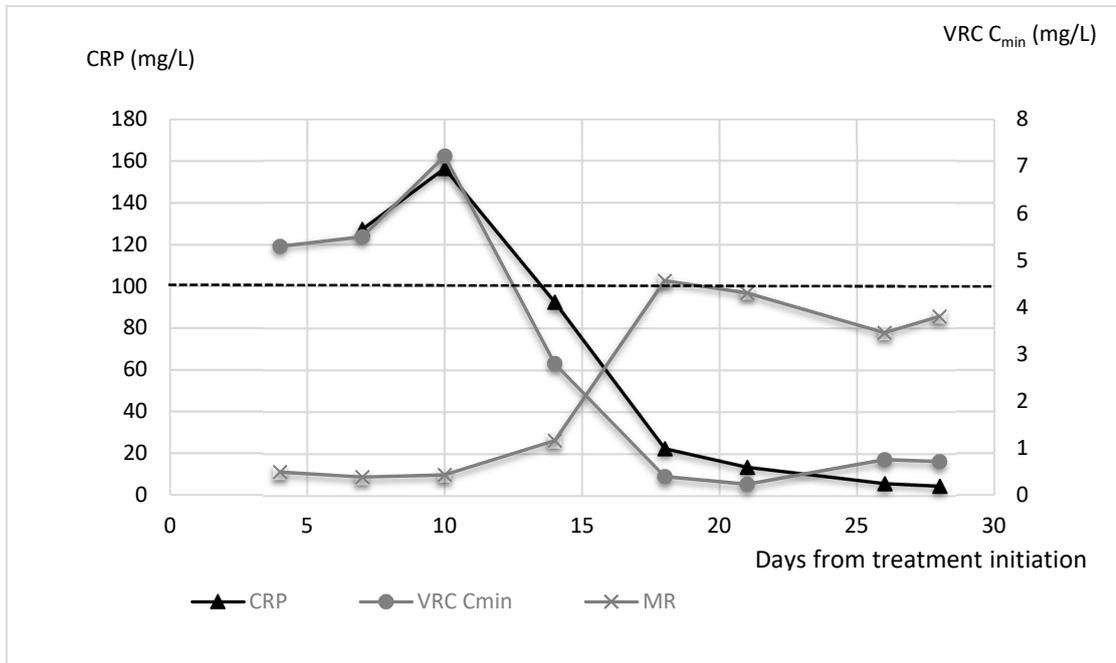
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VRC C_{min}: voriconazole minimum concentration; CRP: C-reactive protein (threshold at 100 mg/L represented by the black dotted line)

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Figure 2. Voriconazole C_{min} and MR changes in parallel with CRP changes: case of a phenoconversion (from Boglione-Kerrien *et al.*¹⁴)



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VRC C_{min}: voriconazole minimum concentration; MR: metabolic ratio; CRP: C-reactive protein (threshold at 100 mg/L represented by the black dotted line)

The genotype of the patient was *17/*17 for CYP2C19, the patient was an ultra-rapid metabolizer of voriconazole. Phenotype and MR determination: MR was measured at 0.43 during the first 10 days (MR < 0.48) and increased towards a very high MR at 4.03 from the 18th day, revealing ultra-rapid metabolism masked by inflammation. This is referred to as phenoconversion.

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TABLES

Table 1. Comparative table of predicted voriconazole C_{min} and MR results, integrating CRP influence

	Mathematical Formula	Bias < 20% on VRC C _{min}	Bias < 20% on MR	Reference
Veringa	VRC +VRC x1.005321 ^N MR-MR x 0.99229 ^N	53% (8/15)	20% (3/15)	[26]
Van Wanrooy	increase 0.015 mg/L VRC C _{min} for every 1 mg/L increase in CRP	53% (8/15)	/	[27]
Encalada Ventura	VRC: increase 0.021mg/L VRC C _{min} for every 1 mg/L increase in CRP. MR : decrease 0.010 mg/L for every 1 mg/L increase in CRP	53% (8/15)	20% (3/15)	[9]
Bolcato	Increase 100 mg/L in CRP: increase of 82% VRC C _{min}	55% (6/11)	/	[25]

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VRC C_{min}: voriconazole minimum concentration; CRP: C-reactive protein; MR: metabolic ratio.

Formulas were tested on n=15 patients from the Boglione-Kerrien et al study¹⁴ (only 11 patients for the Bolcato formula because the increase in concentration was not specified in the event of variation in CRP greater than 100 mg/L with this formula).

The analysis was based on a predicted/measured threshold variation = 20%.