CYP2C19: voriconazole 1683 to 1685

95% CI = 95% confidence interval, ALP = alkaline phosphatase, ALAT = alanine aminotransferase, appr. = approximately, ASAT = aspartate aminotransferase, AUC = area under the concentration-time curve, Cl_{or} = clearance oral, C_{max} = the maximum plasma concentration, CTCAE = common terminology criteria for adverse events, GGT = gamma-glutamyl transpeptidase, IQR = interquartile range, IM = intermediate metaboliser (*1/*2, *1/*3, *17/*2, *17/*3) (reduced CYP2C19 enzyme activity), NM = normal metaboliser (*1/*1, *1/*17) (normal CYP2C19 enzyme activity), NS = not significant, OR = odds ratio, PM = poor metaboliser (*2/*2, *2/*3, *3/*3) (absent CYP2C19 enzyme activity), S = significant, SmPC = summary of product characteristics, $t_{1/2}$ = half-life, UM = ultra-rapid metaboliser (*17/*17) (increased CYP2C19 enzyme activity).

Disclaimer: The KNMP Pharmacogenetics Working Group formulates optimal drug recommendations on the basis of the available evidence. If these optimal recommendations cannot be followed due to practical limitations, e.g. because therapeutic drug monitoring or lower doses are not available, healthcare professionals should consider the best available alternative.

Brief summary and justification of choices:

Summary

The KNMP Pharmacogenetics Working Group concluded that this concerns a gene-drug interaction and that action is required for PM, IM and UM (yes-yes-interactions). For IM, there is insufficient evidence to recommend a dose reduction and only therapeutic drug monitoring is recommended. For PM and UM, there is sufficient evidence to recommend an adjustment of the initial dose. Refer below for the justification of these choices.

Justification of choices

Voriconazole is predominantly metabolised by CYP2C19 and to a lesser extent by CYP2C9 and CYP3A4. Voriconazole inhibits the activity of these three enzymes, resulting in non-linear kinetics for voriconazole. The most important metabolite, voriconazole-N-oxide, is inactive. Children metabolise voriconazole more rapidly than adults and the non-linear kinetics start at higher doses in children than in adults.

Voriconazole has a narrow therapeutic range. The NVZA mentions the following therapeutic ranges: pulmonal aspergillosis 1-6 µg/mL, badly penetrable areas such as cerebral infection, sinus infection 2-6 µg/mL. The NVZA indicates that it is recommended to lower the upper limit to 4 µg/mL in case of impaired liver function, In addition, the NVZA states that the role of therapeutic drug monitoring (TDM) of voriconazole only applies to Aspergillus species sensitive to voriconazole. There are no data on application of TDM in case of infections caused by yeast and other moulds, such as Scedosporium and Fusarium, or caused by less sensitive or resistant strains of Aspergillus fumigatus. Finally, the NVZA states that indications for target values for prophylaxis are lacking up to now. At the moment, for prophylaxis, the therapeutic limit of > 1 µg/mL is used. The risk of voriconazole-induced hepatotoxicity and other side effects increases with concentrations higher than 4 µg/mL.

Several studies found a relatively high percentage of subtherapeutic trough concentrations at normal doses for NM. In one study, the trough concentrations for 48 NMs at standard voriconazole dose were < 1,5 µg/mL in 50% of cases and > 5.5 µg/mL in 10.4% of cases (Miao 2019). In another study, the trough concentrations for 59 NM at a dose of 200-250 mg 2x daily were < 1 µg/mL in 36% of cases and > 4 µg/mL in 11% of cases (Chuwongwattana 2016). In a third study with standard initial dose, the first trough concentrations for 39 NM (37x *1/*1, 2x *1/*17) were < 1 µg/mL in 33% of cases and > 5.5 µg/mL in 13% of cases (Kim 2013). Despite therapeutic drug monitoring, the incidence of subtherapeutic and supratherapeutic trough concentrations throughout this study was 64% and 28% respectively. In a fourth study, 56% of the first three trough concentrations were < 1.7 µg/mL and 44% < 1 µg/mL for 6 NMs with a normal intravenous initial dose followed by dose adjustment based on therapeutic drug monitoring (Weigel 2015). A fifth study found a median trough concentration on days 7 and 14 that was smaller than 1 µg/mL (0.88 µg/mL and 0.74 µg/mL) for 4 NMs with a standard intravenous dose (6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily) (Brüggemann 2010). In Asian studies, the large majority of NMs has genotype *1/*1. Also in studies reporting data for *1/*1 separately, a relatively high percentage of subtherapeutic trough concentrations at normal doses was found for this genotype. Two studies with genotype-guided therapy for *1/*17 and UM also found a relatively high percentage of subtherapeutic trough concentrations for *1/*1 on normal dose. Hicks 2020 found 30.8% of 13 *1/*1 to have a subthe-

rapeutic voriconazole concentration (< 1 µg/mL) on a standard dose of 200 mg twice daily, and Patel 2020 50% of 30 *1/*1. For both studies, percentage of *1/*1 on standard dose being subtherapeutic was higher than for *1/*17 or *1/*17+UM on a dose of 300 mg twice daily (16.2% for *1/*17 in Hicks 2020 and 15.6% for 29 *1/*17 plus 3 UM in Patel 2020). This suggests that also increasing the dose for *1/*1 (so increasing the dose for NM instead of *1/*17 (with for instance 25% of the normal dose)) might further improve the result of genotype-guided therapy. A third study found 29% of 34 *1/*1 to have a subtherapeutic concentration (< 1 µg/mL) on standard dose, while only 2.9% had a supratherapeutic concentration (> 5.5 µg/mL) (Blanco-Dorado 2020). A fourth study involving patients aged 15-40 years found a required dose for a trough concentration in the therapeutic range (1-2 µg/mL) for 6 *1/*1 that was higher than the standard dose (6.8 versus 4 mg/kg 2x daily and 317 versus 200 (or 100 for patients < 40 kg) mg 2x daily) (Berge 2011).

Genotype-guided therapy with a higher initial dose for NM and for IM or genotype unknown (7 and 6 mg/kg 2x daily respectively instead of 5 mg/kg 2x daily), followed by therapeutic drug monitoring performed in a group of children and adolescents (median age 10.9 years; 11 NM, 7 IM, 2 unknown) resulted in a reduction by a factor 4.5 in the median time required to achieve therapeutic trough concentrations (1-5.5 µg/mL) (Teusink 2016). However, both the dose in the non-genotype-guided group (5 mg/kg 2x daily) and the maximum dose in the genotype-guided group were lower than recommended in the Kinderformularium for children younger than 12 years (9 mg/kg 2x daily orally and 8 mg/kg 2x daily intravenously).

PM and IM: A study showed a higher risk of adverse events for 11 PM (OR = 112 (95% CI: 6-2083)), but only after correction for voriconazole trough concentration in binary analysis, and not in univariate analysis (Zhao 2021). The result only occurring after correction for voriconazole trough concentration makes this result mechanistically unlikely. Because CYP2C19 is a metabolic enzyme, CYP2C19 PM can only increase adverse events via its effect on the plasma concentration. So, correction for the voriconazole trough concentration should abolish any CYP2C19 PM effect instead of revealing it. Zhao 2021 did not find an effect on adverse event risk for 40 IM. A meta-analysis and 16 other studies did not find an effect of the CYP2C19 phenotype on side effects, including hepatotoxicity (Li 2016 (a total of 176 IM and 49 PM for all side effects, 136 IM and 37 PM for hepatotoxicity, 74 IM and 20 PM for neurotoxicity), Hicks 2020 (56 IM, 7 PM), Song 2020 (21 IM, 4 PM), Blanco-Dorado 2020 (20 IM, 1 PM), Yamada 2019 (33 IM, 10 PM), Sienkiewicz 2018 (15x IM), Wang 2016 (24 IM, 8 PM), Mori 2015 (age 2-15 years, 10 IM, 2 PM), Wang 2014 (62 IM, 17 PM), Liu 2014 (48 IM and 7 PM for hepatic side effects, 39 IM and 5 PM for psychiatric side effects), Zonios 2014 (19 IM, 4 PM), Kim 2013 (50 IM, 15 PM), Kim 2011 (17 IM, 2 PM), Berge 2011 (10 IM), Brüggemann 2010 (6 IM), Matsumoto 2009 (19 IM+PM), and Levin 2007 (23 IM+PM)).

A meta-analysis found an increase in treatment response for PM, but not for IM (Li 2016 (149 IM, 33 PM)). Four separate studies did not find an effect of IM and PM on effectiveness (Patel 2020 (23 IM, 4 PM), Wang 2014 (62 IM, 17 PM), Liu 2014 (35 IM, 7 PM), and Kim 2013 (50 IM, 15 PM)).

One study with 50 IM and 15 PM found a higher percentage of patients with a therapeutic first trough concentration (1-5.5 µg/mL) and a lower percentage of patients with a subtherapeutic first trough concentration (< 1 µg/mL), but no effect on the percentage of patients with a supratherapeutic concentration (> 5.5 µg/mL), for IM and PM (Kim 2013). In a study involving 42 IM and 14 PM and a dose of 200-250 mg 2x daily, the distribution over the trough concentration groups (< 1 µg/mL, 1-4 µg/mL and > 4 µg/mL) was different for IM+PM (fewer low and more high trough concentrations) than for NM (Chuwongwattana 2016). Similarly, Miao 2019 found a different distribution over the trough concentration ranges (< 1.5 µg/mL, 1.5-5.5 µg/mL and > 5.5 µg/mL) for 44 IM and 14 PM compared to NM, with IM and PM showing more supratherapeutic and less subtherapeutic concentrations. A study with 23 IM and 4 PM found the percentage patients with subtherapeutic trough concentration (< 1 µg/mL) to be lower for IM and PM than for NM (Patel 2020). A study with 20 IM and 1 PM found the mean voriconazole trough concentration to be supratherapeutic for PM and therapeutic for IM and NM (Blanco-Dorado 2020). A study found for 10 IM a lower dose required to achieve therapeutic trough concentrations, but a study with 6 IM and a study with 10 IM and 2 PM (children or young adults) did not (Berge 2011, Lamoureux 2016 and Teusink 2016).

The manufacturer does not recommend dose adjustment, because there is no clear relationship between plasma concentration and effectiveness. The risk of hepatotoxicity as a side effect of voriconazole increases with higher concentrations, but it is not possible to give a cut-off point for the plasma concentration, because the occurrence of hepatotoxicity is highly individual. Furthermore, the range of plasma concentrations in a group of NMs is already very broad. However, in Mikus 2006, the authors state that hepatotoxicity is a dose-limiting side effect and is concentration-dependent. Every increase in plasma concentration of 1 mg/L is thought to increase the incidence of liver dysfunction by 7-17%. In addition, Matsumoto 2009 postulates a relatively narrow therapeutic range (a trough concentration of 2-4 mg/L). They base the upper limit on a strongly increased incidence of hepatotoxicity at trough concentrations > 4 mg/L.

According to hospital pharmacists with a lot of experience with voriconazole, the non-linear pharmacokinetics of voriconazole make it difficult to calculate the effect of a dose reduction. Furthermore, the exposure in patients is often much lower than in volunteers who receive a comparable dose and voriconazole concentrations have a tendency to decrease over time.

In addition to the non-linear pharmacokinetics, the presence of several factors influencing voriconazole metabolism in a CYP2C19-dependent manner contributes to uncertainty in required dose reduction. Increasing

age is well known to correlate with decreasing CYP2C19 activity, leading to a higher dose requirement in children and possibly, a lower dose requirement in the elderly (see also Shang 2020). In addition, inflammation (as measured by C-reactive protein levels) inhibits voriconazole metabolism, resulting in an increased risk of overexposure. A meta-analysis showed this effect to be higher in NM+UM than IM+PM, suggesting that inhibition of CYP2C19 is involved (Bolcato L et al. Combined impact of inflammation and pharmacogenomic variants on voriconazole trough concentrations: a meta-analysis of individual data. J Clin Med 2021;10:2089. PMID: 34068031). Inhibition of CYP2C19 by older age or inflammation results in interindividual differences in the CYP2C19 activity in NM and so, in age- and inflammation-dependent variations in the difference in metabolic activity between NM and PM.

As a meta-analysis found an increased effectiveness for PM, the KNMP Pharmacogenetics Working Group decided not to recommend a dose reduction for PM and IM, which would result in comparable plasma concentrations as in NM at a normal dose. As one study found a higher incidence of trough concentrations > 4 µg/mL for PM and IM and as there were large differences in the dose-corrected trough concentrations within each of the phenotype groups, therapeutic drug monitoring is recommended for both IM and PM (yes/yes-interactions). An excessively high dose over a period of one week does not result in increased effectiveness, but can cause side effects. The meta-analysis found no increased risk of side effects, including hepatotoxicity, for IM and PM. However, hepatotoxicity is expressed in many forms and is therefore not easy to measure. It occurs rapidly and although there is no cut-off value, there is a strong relationship between exposure and effect. For these reasons, a lower initial dose is recommended for PM, as they have the highest risk of an excessively high plasma concentration. The recommendation will take into consideration that voriconazole is seldom if ever started in a primary care setting.

UM: A study showed all 3 UM to have therapeutic voriconazole trough concentrations (1-5.5 µg/ml) on a dose of 300 mg twice daily (1.5 times the standard dose) (Patel 2020). Despite the therapeutic concentrations, 2 of the UM experienced a grade 3 adverse event. A study showed all 3 UM to have subtherapeutic voriconazole concentrations (< 2 µg/ml) on standard dose (a loading dose of 6 mg/kg every 12 hours during day 1 and a maintenance dose of 4 mg/kg every 12 hours) (Hamadeh 2017). Increasing the dose with 25% to 5 mg/kg in 2 of the UM resulted in voriconazole trough concentrations of 2.4 µg/mL and 1.85 µg/mL, respectively. No hepatotoxicity or other adverse effects were observed following dose increase. In this study, the first voriconazole trough concentration for UM on standard dose was decreased by 63% compared to NM. A study showed both UM to have a subtherapeutic concentration (< 1 µg/mL) on standard dose (Blanco-Dorado 2020). A study with 4 UM found an increase in the dose required to achieve a therapeutic trough concentration (1-5 µg/ml) by a factor of 2 (Lamoureux 2016). The determined required dose was 6.75 mg/kg twice daily (1.7-fold the standard dose). This study found a decrease in the daily dose-corrected and weight-corrected trough concentration by 85% compared to *1/*1. There was no significant difference in the uncorrected trough concentrations in this study in which the dose was adjusted based on therapeutic drug monitoring. Chawla 2015 reported 1 UM to achieve trough concentrations in the therapeutic range (2-6 µg/mL) with a standard weight-based dose. A study involving patients aged 13-76 years, of which 4 UMs, found no effect on the trough concentration at the standard dose followed by clinical adjustment (Zonios 2014). In this study, using doses ranging from approximately 2.3 to 9.3 mg/kg twice daily, the mean trough concentration for UM was therapeutic (3.6 µg/ml). In one study, all 4 paediatric UMs had mean subtherapeutic trough concentrations (< 1 µg/mL) (Hicks 2014). However, the initial dose in this study was lower for most of the patients than the dose in the Kinderformularium (7 instead of 8-9 mg/kg 2x daily), and the trough concentration did increase in these patients after a dose increase. This study found a decrease in the median dose-corrected trough concentration by 86% compared to *1/*1. Berge 2011 found for 7 *1/*17 plus 1 UM that the median time to the first trough concentration within the therapeutic range (1-2 µg/mL) was extended and that the percentage of subtherapeutic trough concentrations (< 0.5 µg/mL) during the first 42 days of treatment was increased, both by a factor of 2.4. For the UM, the dose required for therapeutic concentrations (1-2 µg/mL) was approximately 1.3-fold that for *1/*1. The determined required dose was approximately 8.8 mg/kg twice daily intravenously and 412 mg twice daily orally (approximately twice the standard dose). A study in patients aged 2-12 years found an insignificant 2.5-fold increase in median $AUC_{0\text{-}12h}$ for 2 UM compared to *1/*1 (Driscoll 2011;55: 5770-9).

Not a single study found a significant effect of the UM phenotype or UM+*1/*17 on side effects (Blanco-Dorado 2020 (2 UM), Sienkiewicz 2018 (3 UM), Williams 2016 (11 UM, 45 *1/*17), and Berge 2011 (1 UM, 7 *1/*17)). Neither the meta-analysis nor the four studies on effectiveness included UM on normal dose in the analysis (Li 2016, Patel 2020, Wang 2014, Liu 2014, and Kim 2013). However, Patel 2020 found a dose increase with 50% in 3 UM and 29 *1/*17 and a standard dose in the other genotypes to both decrease the percentage of patients with subtherapeutic voriconazole concentration (both for all patients and for *1/*17+ UM, with 42% and 78% respectively) and increase the voriconazole success rate (including voriconazole tolerance) (with 45% in all patients) compared to a historical control on standard dose. As there are indications that there is an increased risk of subtherapeutic trough concentrations and consequently reduced effectiveness for UM, the KNMP Pharmacogenetics Working Group decided to recommend a higher initial dose followed by therapeutic drug monitoring (yes/yes-interaction).

An overview of the observed clinical and kinetic effects per phenotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system. A substantiation of the dose recommendation for PM and UM is provided below.

Justification of dose recommendation

Voriconazole has non-linear kinetics at therapeutic doses. In addition, therapeutic drug monitoring is performed based on the trough concentration. Therefore, the dose adjustment for voriconazole was calculated in a different manner than we would normally perform this calculation for other medicines. Standard procedure is to use the AUC first. If this value is not available, we use the steady-state plasma concentration and if this value is also not available, we use the clearance. However, for voriconazole, we first used the dose required to achieve a trough concentration within the therapeutic range, if this value was not available then we used the steady-state (trough) concentration and if this value was not available, we used the AUC.

PM: For PM, three studies (one with 17, one with 11 and one with 1 PM) determined the mean kinetic parameter for adults compared to NM (Yuan 2020, Lamoureux 2016, and Wang 2014). The study with 1 PM involved the required dose, but the larger studies involved the trough concentration. The weighted mean in these 3 studies was a dose reduction to 53% of the standard dose (range 53-54%; median 53%).
Eight studies with a total of 90 PM determined median kinetic parameters for adults compared to NM (Shang 2020, Yamada 2019, Mafuru 2019, Chuwongwattana 2016, Chawla 2015, Yamada 2015, Kim 2013, and Kim 2011). All eight studies determined the trough concentration or AUC. The weighted mean in these 8 studies was a reduction of the dose to 63% of the standard dose (range 33-96%; median 65%).
For children, only 1 study with 2 PM determined the mean trough concentration compared to NM (Mori 2015). The calculated dose adjustment based on this study was a reduction of the dose to 23% of the standard dose.
Four studies with a total of 13 PM determined median kinetic parameters of children for PM compared to NM (Tian 2021, Teusink 2016, Hicks 2014, and Driscoll 2011;55:5780-9). One study with 2 PM determined the required dose, the other three determined either the trough concentration or the AUC. The weighted mean of the dose increase calculated based on these parameters was a reduction to 38% of the standard dose (10-107%; median 32%).
The percentages that were found are based on very small numbers of PM and studies. Furthermore, a large variation in the values was found for children and for the median parameters of adults. Most of the values appear to indicate a reduction of the dose to 40-60% in order to achieve a plasma concentration comparable to NM at the standard dose. However, the value found based on the average trough concentration in children (23% of the standard dose) appear to correspond well to the 4 times higher exposure found in healthy volunteers according to the SmPC. For this reason, a dose reduction to 50% of the normal dose was selected to compensate or partially compensate for the higher exposure in PM.

UM: For UM, three studies with a total of 8 UM determined the mean kinetic parameter for adults versus NM (Lamoureux 2016, Berge 2011 (15-40 years), and Hamadeh 2017). Two studies with 4 and 1 UM determined the required dose, and the third study with 3 UM the trough concentration. The weighted mean in these 3 studies was an increase in the dose to 220% of the standard dose (range 127-272%; median 204%).
For children, only median kinetic parameters were determined for UM versus NM (3 studies, total of 7 UM, one study determined the trough concentration, two studies determined the AUC) (Hicks 2014, Driscoll 2011; 55:5770-9, and Driscoll 2011;55:5780-9). The weighted mean of the dose increase determined based on these parameters was an increase in the dose to 374% of the standard dose (41-600%; median 135%).
The determined percentage of 220% for adults is based on a very limited number of UMs. In addition, if only the more reliable required dose data are included, the values would be considerably lower (weighted mean 188% of the standard dose (range 127-204%; median 165%). In addition, Hicks 2020 showed a 1.5-fold higher dose in *1/*17 to result in a 4,5-fold higher trough concentration, and Patel 2020 showed all of 3 UM to have therapeutic trough concentrations on a 1.5-fold higher dose. For this reason, the smallest weighted mean of 188% was chosen and rounded down to 150%, which is easier to use in practice. The same dose increase is recommended for children. The dose increase calculated for children exhibited a much greater distribution and was also determined based on the assumption of linear kinetics. Therefore, this value is too unreliable to be able to conclude from it that the required dose increase for children differs from that of adults.

Recommendation concerning pre-emptive genotyping, including justification of choices:

The KNMP Pharmacogenetics Working Group considers genotyping before starting voriconazole to be potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.

The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):

No severe clinical effects were observed in users of voriconazole with a variant phenotype. The maximum severity code was C corresponding to CTCAE grade 2. This results in a score of 0 out of the maximum of 2 points for the first

criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) of voriconazole indicates that voriconazole exposure is 4-fold higher in CYP2C19 PM and 2-fold higher in CYP2C19 IM than in CYP2C19 NM, but neither mentions PM or IM as a contra-indication for voriconazole nor recommends pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).
Note: Whereas according to the clinical implication score only genotyping of individual patients has to be considered and despite the lack of proof for a diminished effectiveness of voriconazole in patients with *1/*17 and UM genotypes, two cost effectiveness studies suggest that CYP2C19 genotype-guided treatment with *1/*17 and UM receiving 1.5-fold the standard dose or either an increased dose or alternative, to be both cheaper and more effective than non-genotype-guided treatment (Patel 2020 and Mason 2015).

The table below follows the KNMP definitions for NM, PM, IM and UM. The definitions of NM, PM, IM and UM used in the table below may therefore differ from the definitions used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Tian X et al.
Impact of CYP2C19 phenotype and drug-drug interactions on voriconazole concentration in pediatric patients.
Antimicrob Agents Chemother 2021;65:e0020721.
PMID: 34152823.</td><td>3

PM: A
IM: A</td><td>65 immunocompromised paediatric patients were treated with voriconazole, of whom approximately 12% prophylactically. Voriconazole doses ranged from approximately 0.5 mg/kg to approximately 14.5 mg/kg.
Steady state voriconazole trough concentrations were determined. 82% of patients had a voriconazole trough concentration within the therapeutic range (0.5-5 µg/mL).
Comedication with effect on CYP2C19 and voriconazole metabolism was not excluded.

Genotyping:
- 1x *1/*17
- 21x *1/*1
- 26x IM
- 8x PM

Results:
<table>
<tr><td colspan="5">Results compared to *1/*1:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>*1/*17</td><td>value for *1/*1</td></tr>
<tr><td>median dose- and weight-corrected voriconazole concentration</td><td>x 4.36 (S)</td><td>x 2.82 (S)</td><td>x 0.82 (NS)</td><td>0.11 µg/mL per mg/kg</td></tr>
<tr><td>dose in patients with therapeutic voriconazole concentrations (0.5-5 µg/mL)</td><td colspan="3">≤ 12 years: NS for IM+PM compared to NM
> 12 years: NS for IM+PM compared to NM</td><td></td></tr>
</table>
Note: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Chinese population.</td><td>Authors' conclusions: "Taken together, it is necessary to pay attention to the impact of CYP2C19 phenotype and drug-drug interactions to achieve optimal therapy."

Median trough concentration$_{steady\ state}$ at a dose of 1-29 mg/kg per day versus *1/*1, children:
IM: 282%
PM: 436%</td></tr>
<tr><td>ref. 2
Zhao YC et al.
Predictors of adverse events and determinants of the voriconazole trough</td><td>3</td><td>92 kidney transplant patients were treated with voriconazole (73% for a suspected infection and 27% for prophylaxis). Patients received a loading dose of 6 mg/kg intravenously or 400 mg orally every 12 hours on day 1, followed by 4 mg/kg intravenously or 200 mg orally every 12 hours for maintenance. The maintenance dose was adjusted</td><td>Authors' conclusions: "In conclusion, predictors of adverse events are CYP2C19 phenotypes, hemoglobin, and voricona-</td></tr>
</table>

<table>
<tr>
<td>concentration in kidney transplantation recipients. Clin Transl Sci 2021;14:702-11. PMID: 33202102.

ref. 2, continuation</td>
<td>PM: C

IM: A</td>
<td>based on clinical reactions and results of therapeutic drug monitoring.
A mean of 2.3 voriconazole trough concentrations per patient was obtained.
82.8% of patients experienced adverse events. 91% of adverse events occurred within 3 days. Hallucinations (64%), insomnia (56%), and visual impairment (44%) were common adverse events. 65% of patients with adverse events had only one adverse event.
79% of patients with an suspected infection showed an apparent clinical effect of voriconazole.
Comedication with rifampicin, amobarbital, phenobarbital, efavirenz, and ritonavir was excluded, but other comedication with effect on CYP2C19 and voriconazole metabolism was not. Comedication with tacrolimus, cyclosporine and ilaprazole was more frequent in patients with adverse events than in patients without adverse events. Effects of comedication were investigated and, if necessary, adjusted for in regression analysis.
Binary logistic regression analysis of adverse events adjusted for voriconazole trough concentration, tacrolimus use, cyclosporine use, moxifloxacin use, ilaprazole use, and haemoglobin range.
Multiple linear regression analysis of voriconazole trough concentration adjusted for sex, age, weight, postoperative time, tacrolimus use, ilaprazole use, haemoglobin, platelets, alanine transaminase, direct bilirubin, and creatinine.

Genotyping:
- 41x NM
- 40x IM
- 11x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with adverse events</td><td>NS in univariate analysis, and OR = 112 (95% CI: 6-2083) (S) in binary logistic regression analysis adjusting for voriconazole trough concentration</td><td>NS in univariate analysis and in binary logistic regression analysis adjusting for voriconazole trough concentration</td><td>82.9%</td></tr>
<tr><td>voriconazole trough concentration</td><td>appr. x 1.8 (S) in univariate analysis, and S in multivariate analysis</td><td>appr. x 1.2 (S) in univariate analysis (not compared to NM in multivariate analysis)</td><td>appr. 2.2 µg/mL</td></tr>
<tr><td rowspan="2">voriconazole daily dose</td><td>appr. x 0.90</td><td>appr. x 0.97</td><td rowspan="2">appr. 389 mg</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
</table>
</td>
<td>zole trough concentration. Determinants of the voriconazole trough concentration were CYP2C19 phenotypes, platelet count, hemoglobin, concomitant use of ilaprazole.”</td>
</tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td></td><td>Note: This study did not find a correlation of voriconazole trough concentration with voriconazole daily dose.

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this Chinese population. The only patient with *17 (genotype *1/*17) was excluded from the CYP2C19 analyses.</td><td></td></tr>
<tr><td>ref. 3
Shang S et al.
Effect of CYP2C19 polymorphism on the plasma voriconazole concentration and voriconazole-to-voriconazole-N-oxide concentration ratio in elderly patients.
Mycoses
2020 May 16 (online ahead of print).
PMID: 32416606.</td><td>3

PM: A

IM: A</td><td>129 patients with proven or probable invasive fungal infection, of whom 71 aged ≥ 60 years (median 74 years) and 58 aged 18-60 years (median 40 years), were treated with voriconazole. 88.9% of patients ≥ 60 years and 96.6% of patients aged 18-60 years received voriconazole intravenously. The median voriconazole dose was 8.87 mg/kg per day in the patients ≥ 60 years and 7.59 mg/kg per day in the patients of 18-60 years.
Steady state voriconazole trough concentrations were determined.
Comedication with other antifungal drugs and strong enzyme inducers and inhibitors was excluded, but moderate or weak inducers and inhibitors were not.

Genotyping:
18-60 years: - 26x NM; - 27x IM; - 5x PM
≥ 60 years: - 29x NM; - 30x IM; - 12x PM

Results:
<table>
<tr><td colspan="5">Results compared to NM:</td></tr>
<tr><td></td><td>age group (years)</td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td rowspan="3">median dose- and weight-corrected voriconazole concentration (µg/mL per mg/kg)</td><td rowspan="2">18-60</td><td>x 2.16 (S)</td><td>x 1.76 (trend: p = 0.070) (NS)</td><td rowspan="2">0.38</td></tr>
<tr><td colspan="2">Trend for PM versus IM versus NM (p = 0.051) (NS).</td></tr>
<tr><td>≥ 60</td><td>x 1.16 (NS)</td><td>x 1.14 (NS)</td><td>0.64</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM.</td></tr>
<tr><td rowspan="3">median voriconazole concentration (µg/mL)</td><td rowspan="2">18-60</td><td>x 2.02 (S)</td><td>x 1.66 (S)</td><td rowspan="2">2.89</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM.</td></tr>
<tr><td>≥ 60</td><td>NS</td><td>NS</td><td>5.46</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM.</td></tr>
<tr><td rowspan="3">median dose (mg/kg per day)</td><td rowspan="2">18-60</td><td>NS</td><td>trend for a decrease (p = 0.067) (NS)</td><td rowspan="2">7.55</td></tr>
<tr><td colspan="2">NS for PM versus IM versus NM.</td></tr>
<tr><td>≥ 60</td><td>NS</td><td>NS</td><td>8.00</td></tr>
<tr><td colspan="3">NS for PM versus IM versus NM.</td></tr>
<tr><td colspan="5">The median dose- and weight-corrected voriconazole trough concentration was higher in the age group ≥ 60</td></tr>
</table></td><td>Authors' conclusions: "Voriconazole C_0, C_0/dose and C_0/C_N ratio are not significantly affected by the CYP2C19*2/*3 polymorphisms in the elderly patients."

Median trough concentration$_{steady\ state}$ at a median dose of 7.59 mg/kg per day versus NM, 18-60 years:
IM: 176%
PM: 216%

Median trough concentration$_{steady\ state}$ at a median dose of 7.59 mg/kg per day versus NM, ≥ 60 years:
IM: 114%
PM: 116%</td></tr>
</table>

ref. 3, continuation		years than in the age group 18-60 years (S), This difference was significant for NM (x 1.68) (S), smaller and non-significant for IM (x 1.09) (NS), while the effect was numerically opposite for PM (x 0.90) (NS). Note: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Chinese population. Only two patients with *17 were found (one *2/*17 aged 18-60 years and one *1/*17 aged ≥ 60 years), who were not included in the analysis.	
ref. 4 Yuan ZQ et al. The impact of plasma protein binding characteristics and unbound concentration of voriconazole on its adverse drug reactions. Front Pharmacol 2020;11:505. PMID: 32390847.	3 PM: A	Patients with malignant haematological disease were treated with voriconazole for suspected fungal infection or prophylaxis. All patients received a voriconazole loading dose of 6 mg/kg every 12 hours on the first day, followed by a maintenance dose of 4 mg/kg every 12 hours. Steady state voriconazole trough concentrations were determined and values were reported for 26 NM and 11 PM. Comedication with effect on CYP2C19 and voriconazole metabolism was not excluded. Genotyping: - 26x NM - 11x PM Results: Voriconazole trough concentration compared to NM (0.71 µg/mL): PM: x 1.90 (S) Note: Genotyping was for *2, *3, and *17. These are the most important gene variants in this Chinese population. The authors do not mention whether any *17 alleles were found in this patient group.	Authors' conclusions: "The minimum $C_{unbound}$ in steady state of PMs were significantly higher than those of NMs in our result. The similar relationship appeared in minimum C_{total}." Trough concentration$_{steady\ state}$ at a dose of 8 mg/kg per day versus NM: PM: 190%
ref. 5 Hicks JK et al. Prospective CYP-2C19-guided voriconazole prophylaxis in patients with neutropenic acute myeloid leukemia reduces the incidence of subtherapeutic antifungal plasma concentrations. Clin Pharmacol Ther 2020;107:563-70. PMID: 31549389.	3	176 neutropenic acute myeloid leukaemia patients were treated with genotype-guided prophylactic voriconazole. Voriconazole was avoided in UM, voriconazole 300 mg twice daily was used in *1/*17 and the standard dose of 200 mg twice daily was used for *1/*1, IM and PM. UM patients received isavuconazol instead. Another 26 neutropenic acute myeloid leukaemia patients did not receive genotype-guided prophylactic voriconazole despite recommendation. Main reasons for this were discharge from hospital before genotyping result known (54%), unknown (23%), and elevated liver enzymes (11.5%). Voriconazole trough concentrations were obtained in 70 patients. Genotype groups in the prophylactically treated patients differed significantly with respect to sex. Relevant comedication was not excluded. Correction for proton pump inhibitor use was for the whole group, not for the CYP2C19 inhibitory ones (omeprazole and esomeprazole) separately. Genotyping: Genotype-guided group: - 3x UM; - 46x *1/*17 Not genotype-guided group: - 1x UM; - 12x *1/*17 Group with trough concentrations: - 41x *1/*17	Authors' conclusions: "Interventional voriconazole resulted in higher plasma trough concentrations (median 2.7 µg/mL) compared to the standard prophylactic dosage (median 0.6 µg/mL. Subtherapeutic concentrations were avoided in 83.8% of CYP2C19 rapid metabolizers receiving interventional dosage compared to 46.2% receiving standard dosage. CYP-2C19 genotyping to preemptively guide prophylactic voriconazole dosing is feasible and may be a potential strategy for reducing the risk of subtherapeutic trough concentrations

<table>
<tr>
<td>ref. 5, continuation</td>
<td>Genotype-guided versus not genotype-guided therapy: *1/*17: A all patients: AA

IM: AA
PM: AA</td>
<td>
- 64x *1/*1 - 11x *1/*1 - 13x *1/*1
- 56x IM - 2x IM - 11x IM
- 7x PM - 5x PM

Results:
<table>
<tr><td colspan="3">Results for genotype-guided therapy compared to not genotype-guided therapy (historical control for infections):</td></tr>
<tr><td></td><td></td><td>value for not genotype-guided or historical control group</td></tr>
<tr><td>median voriconazole trough concentration for *1/*17</td><td>x 4.50 (S)</td><td>0.6 µg/ mL</td></tr>
<tr><td>% of *1/*17 with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 0.30 (S)</td><td>53.8%</td></tr>
<tr><td rowspan="2">nodular pneumonia cases per 1000 neutropenic days</td><td>NS</td><td rowspan="2">2.2 cases per 1000 days</td></tr>
<tr><td>None of the 4 UM on isavuconazole had a breakthrough fungal infection.</td></tr>
<tr><td colspan="3">Six *1/*17 receiving voriconazole 300 mg twice daily had supratherapeutic troughs (ranging from 6-8.7 µg/mL). One patient experienced neurotoxicity, one patient had an increase in liver enzymes, and 4 patients did not have a toxicity necessitating voriconazole discontinuation.</td></tr>
</table>
<table>
<tr><td colspan="6">Results compared to *1/*1 on voriconazole 200 mg twice daily (400 mg):</td></tr>
<tr><td></td><td>*1/*17 400 mg</td><td>*1/*17 600 mg</td><td>IM</td><td>PM</td><td>value for *1/*1</td></tr>
<tr><td rowspan="2">median voriconazole trough concentration</td><td>x 0.23</td><td>x 1.04</td><td>x 0.81 (*1/*2), x 0.73 (*2/*17)</td><td>x 0.73</td><td>2.6 µg/ mL</td></tr>
<tr><td colspan="4">Significance was not determined compared to *1/*1, only for *1/*17 compared to (*1/*1+IM+ PM).</td></tr>
<tr><td rowspan="3">% of patients with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 1.75</td><td>x 0.53</td><td>x 0</td><td>x 0</td><td rowspan="3">30.8 %</td></tr>
<tr><td colspan="4">Significance was not determined compared to *1/*1, only for *1/*17 600 mg compared to *1/*17 400 mg.</td></tr>
<tr><td colspan="4">Note: Although the authors state that no PM had subtherapeutic concentrations, the trough concentration figures do show a subtherapeutic concentration for PM.</td></tr>
<tr><td>% of patients discontinuing voriconazole due</td><td></td><td colspan="3">NS for *1/*17 600 mg versus *1/*1 versus IM versus PM</td><td>21.9 %</td></tr>
</table>
</td>
<td>that potentiate breakthrough fungal infections.”</td>
</tr>
</table>

<table>
<tr><td>ref. 5, continuation</td><td></td><td>
<table>
<tr><td>to neuro-toxicity</td><td></td><td></td><td></td></tr>
<tr><td>% of patients discontinuing voriconazole due to elevated liver transaminases</td><td></td><td>NS for *1/*17 600 mg versus *1/*1 versus IM versus PM</td><td>10.9 %</td></tr>
</table>

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this population from the USA. *3 was not found in this patient group.</td><td></td></tr>
<tr><td>ref. 6
Patel JN et al.
Evaluation of CYP-2C19 genotype-guided voriconazole prophylaxis after allogeneic hemato-poietic cell trans-plant.
Clin Pharmacol Ther 2020;107:571-9.
PMID: 31549386.</td><td>3</td><td>89 allogeneic hematopoietic cell transplant recipients were treated with genotype-guided prophylactic voriconazole. A voriconazole dose of 300 mg twice daily was used in *1/*17 and UM, and the standard dose of 200 mg twice daily was used for *1/*1, IM and PM. Follow-up was for the first 100 post-transplant days. On the first post-transplant day, intravenous micafungin was started. Within about 1 week post-transplant, this was switched to oral voricona-zole. Dose titration was based on therapeutic drug monito-ring.
Voriconazole success rate could be analysed in 78 patients. Voriconazole prophylaxis success rate was defi-ned as the absence of intolerance to voriconazole (≤ 14 total days of interruption due to drug-related toxicities), the absence of a proven/probable invasive fungal infection, and surviving from start of voriconazole to the 100th post-transplant day.
No patients experienced a proven or probable invasive fungal infection. 40.5% experienced at least one adverse event possibly related to voriconazole. 5.6% experienced a grade 3 adverse event, and 13.5% discontinued voricona-zole due to an adverse event. The most frequent adverse events included elevated alkaline phosphatase (28.1%), elevated alanine/aspartate aminotransferase (27.0%), and neurological symptoms (7.9%). 2.2% experienced QTc interval prolongation (> 500 ms) which led to voriconazole discontinuation.
Voriconazole trough concentrations were measured at the first steady-state level (at least 5 days after start of vorico-nazole).
Comedication with omeprazole was not excluded. The authors indicated that prior pharmacokinetic studies demonstrated no clinically relevant interaction, and no trend was identified in this population. Patients did not use other possibly relevant comedication.
A power calculation showed a sample size of 60 evaluable subjects to be required for a power of at least 90% to detect a difference from the historical control rate of 50% for the proportion of subtherapeutic patients, assuming the true subtherapeutic rate is 30%.

Genotyping:
- 3x UM
- 29x *1/*17
- 30x *1/*1</td><td>Authors' conclusions: "CYP2C19 genotype-guided voriconazole dosing reduced subtherapeutic drug concentrations and effectively prevented invasive fungal infections."</td></tr>
</table>

<table>
<tr>
<td>ref. 6, continuation</td>
<td>Genotype-guided versus not genotype-guided therapy:
*1/*17+ UM: A

all patients:
AA#

IM: A
PM: A</td>
<td>
- 23x IM
- 4x PM

Results:
<table>
<tr><td colspan="3">Results for genotype-guided therapy compared to historical controls:</td></tr>
<tr><td></td><td></td><td>value for historical controls</td></tr>
<tr><td>% of patients with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 0.58 (S)</td><td>50%</td></tr>
<tr><td>% of *1/*17+UM with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 0.22 (S)</td><td>appr. 70%</td></tr>
<tr><td>voriconazole success rate (including voriconazole tolerance)</td><td>x 1.45 (S)</td><td>54%</td></tr>
<tr><td colspan="3">Two patients receiving genotype-guided therapy had a supratherapeutic voriconazole concentration (> 5.5 µg/mL) (both *1/*17, both > 7 µg/mL, neither experienced a grade 3 adverse event). So, 6.9% of *1/*17 on voriconazole 300 mg twice daily developed supratherapeutic concentrations.</td></tr>
<tr><td colspan="3">Two UM, one *1/*1, and one IM experienced a grade 3 adverse event.</td></tr>
</table>
<table>
<tr><td colspan="6">Results compared to *1/*1 on voriconazole 200 mg twice daily (400 mg):</td></tr>
<tr><td></td><td>*1/*17 +UM 400 mg[a]</td><td>*1/*17 +UM 600 mg</td><td>IM</td><td>PM</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 1.4</td><td>x 0.31
UM: x 0
S for the comparison between *1/*17+UM 600 mg, *1/*1, IM, and PM.</td><td>x 0.52</td><td>x 0</td><td>50%</td></tr>
<tr><td>voriconazole trough concentration</td><td></td><td>x 2.7
S for the comparison between *1/*17+UM 600 mg, *1/*1, IM, and PM.</td><td>x 1.7</td><td>x 2.3</td><td>1.0 µg/mL</td></tr>
<tr><td>voriconazole success rate (including voriconazole tolerability)</td><td></td><td colspan="3">NS for the comparison between *1/*17+UM 600 mg, *1/*1, IM, and PM.</td><td>71%</td></tr>
<tr><td>voriconazole discontinuation due to adverse events</td><td></td><td>x 1.1
Significance between the groups not determined.</td><td>x 1.3</td><td>x 2.5</td><td>13%</td></tr>
<tr><td colspan="6">[a]: historical controls</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td></td><td>Note: In this study, voriconazole discontinuation due to adverse events did not correlate with voriconazole concentrations.

Note: Genotyping was for *2, *3 and *17. These are the most important gene variants in this population from the USA.</td><td></td></tr>
<tr><td>ref. 7
Song Y et al.
Association of CYP-2C19 and UGT1A4 polymorphisms with voriconazole-induced liver injury.
Per Med 2020;17:15-22.
PMID: 31797717.</td><td>3

PM: AA
IM: AA</td><td>38 patients with proven, probable or possible invasive fungal disease were treated with voriconazole (a loading dose of 6 mg/kg intravenously or 400 mg orally twice on day 1, followed by 4 mg/kg intravenously or 200 mg orally twice daily for maintenance).
10 of these patients (26.3%) developed voriconazole-induced liver injury. Patients developing voriconazole-induced liver injury had a higher body weight, and trends for a higher pre-treatment ALAT and total bilirubin, compared to patients not developing voriconazole-induced liver injury.
Drug-induced liver injury was defined as the level of at least one indicator of liver injury (ALAT, ASAT, ALP or total bilirubin) being higher than the upper limit of normal after the initiation of voriconazole therapy. Causality between liver injury and voriconazole therapy was assessed using the standardized Roussel Uclaf Causality Assessment Method. Patients with abnormal liver function before voriconazole therapy were excluded.
Trough concentrations were determined after at least 2 days of treatment.
Comedication with other hepatotoxic drugs was excluded, but comedication with effect on CYP2C19 and voriconazole metabolism was not.

Genotyping:
- 13x NM
- 21x IM
- 4x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with voriconazole-induced liver injury</td><td>NS</td><td>NS</td><td>15%</td></tr>
<tr><td colspan="4">The mean voriconazole trough concentration in patients with voriconazole-induced liver injury was within the therapeutic range (1-5.5 µg/mL).</td></tr>
</table>
Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.</td><td>Authors' conclusions: "There was no significant correlation between voriconazole-induced liver injury and gene polymorphisms of CYP-2C19 and UGT1A4."</td></tr>
<tr><td>ref. 8
Blanco-Dorado S et al.
Impact of CYP2C19 genotype and drug interactions on voriconazole plasma concentrations: a Spain pharmacogenetic-pharmacokine-</td><td>3</td><td>78 patients were treated with voriconazole for a median of 26 days (4-185 days), mostly for suspected fungal infections (96% of patients). The maintenance dose in patients on oral voriconazole (n = 36) was 200 mg twice daily in all cases. In patients on intravenous voriconazole (n = 42), the mean loading dose was 5.90 mg/kg twice daily and the mean maintenance dose 3.79 mg/kg twice daily.
A voriconazole-related adverse event was defined as one with a possible or strong relationship to the drug treatment.</td><td>Authors' conclusions: "These results suggest the potential clinical utility of using CYP2C19 genotype-guided voriconazole dosing to achieve concentrations in the therapeutic range in the early course of</td></tr>
</table>

<table>
<tr>
<td>tic prospective multi-center study. Pharmacotherapy 2020;40:17-25. PMID: 31782536.

ref. 8, continuation</td>
<td>PM: AA
IM: AA
UM: AA</td>
<td>Steady state voriconazole trough concentrations were determined.
None of the patients with hepatic adverse events received other hepatotoxic drugs, but comedication with effect on CYP2C19 and voriconazole metabolism was not excluded.

Genotyping:
- 2x UM
- 21x *1/*17
- 34x *1/*1
- 20x IM
- 1x PM

Results:
<table>
<tr><td colspan="6">Results compared to *1/*1:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>*1/*17</td><td>UM</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with adverse events</td><td colspan="4">NS for the comparisons between PM, IM, *1/*1, *1/*17 and UM.</td><td>21%</td></tr>
<tr><td>% of patients with subtherapeutic voriconazole concentration (< 1 µg/mL)</td><td>x 0</td><td>x 1.02</td><td>x 1.30</td><td>x 3.40</td><td>29%</td></tr>
<tr><td></td><td colspan="4">Significance was not determined compared to *1/*1, only for *1/*17+UM compared to (*1/*1+ IM+PM).</td><td></td></tr>
<tr><td>% of patients with supratherapeutic voriconazole concentration (> 5.5 µg/mL)</td><td>x 34</td><td>x 1.70</td><td>x 1.62</td><td>x 0</td><td>2.9%</td></tr>
<tr><td></td><td colspan="4">Significance between the groups was not determined.</td><td></td></tr>
<tr><td></td><td colspan="4">Note: Although the authors state that 0% of *1/*17+UM had supratherapeutic concentrations, the trough concentration figure does show a supratherapeutic concentration for *1/*17.</td><td></td></tr>
<tr><td>voriconazole trough concentration</td><td colspan="4">NS for the comparison between PM, IM, *1/*1, *1/*17 and UM.
NS in multivariate linear mixed-effects analysis for *17 and for *2.</td><td>appr. 2.1 µg/ mL</td></tr>
<tr><td></td><td colspan="4">The mean voriconazole trough concentration was supratherapeutic for PM, therapeutic for IM, *1/*1 and *1/*17, and subtherapeutic for UM.</td><td></td></tr>
</table>
Note: Genotyping was for *2-*4, *10 and *17, and for 53 patients also for *5-*8. These are the most important gene variants in this Spanish population.</td>
<td>therapy. Larger studies are needed to confirm the impact of pharmacogenetics on voriconazole pharmacokinetics.”</td>
</tr>
<tr>
<td>ref. 9
Yamada T et al. Impact of flavin-containing monooxygenase 3 and CYP2C19 genotypes on plasma disposition and adverse effects of voriconazole administered orally in immunocompro-</td>
<td>3</td>
<td>65 immunocompromised patients were treated with voriconazole 100-300 mg (median 200 mg) orally twice daily for (suspected) fungal infection (n = 43) or prophylaxis (n = 22). Treatment was for at least 5 days.
4.6% of patients had total bilirubin elevation, 6.2% ASAT elevation, 6.2% ALAT elevation, 6.2% γ-glutamyl transpeptidase aspartate aminotransferase elevation, and 3.1% visual changes. None of the adverse events was severe.
Steady state trough concentrations were determined.
Comedication with strong CYP2C19 or CYP3A4 inducers or inhibitors was excluded, as was inflammation, but come-</td>
<td>Authors’ conclusions: “CYP2C19 phenotype did not affect the plasma concentration and metabolic ratio of voriconazole. …. The FMO3 and CYP2C19 genotypes and their associated voriconazole pharmacokinetics did not have an effect on the inci-</td>
</tr>
</table>

<table>
<tr>
<td>mised patients.
J Infect Chemother 2019;25:1019-25.
PMID: 31239195.

ref. 9, continuation</td>
<td>PM: AA
IM: AA</td>
<td>dication with moderate or weak inducers or inhibitors was not.

Genotyping:
- 22x NM
- 33x IM
- 10x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>% of patients with adverse events</td><td colspan="2">NS for CYP2C19 phenotype in multiple regression analysis</td><td></td></tr>
<tr><td>median dose- and weight-corrected voriconazole concentration</td><td>x 1.04 (NS)</td><td>x 1.53 (NS)</td><td>0.51 µg/mL per mg/kg</td></tr>
</table>
Note: In this study, adverse events did not correlate with voriconazole concentrations.

Note: Genotyping was for *2 and *3. These are the most important gene variants in this Japanese population.</td>
<td>dence of adverse effects.”

Median dose- and weight-corrected trough concentration$_{steady\ state}$ at a dose of 200-600 mg/day versus NM:
IM: 153%
PM: 104%</td>
</tr>
<tr>
<td>ref. 10
Mafuru M et al.
The influence of proinflammatory cytokines on voriconazole trough concentration in patients with different forms of hematologic disorders.
J Clin Pharmacol 2019;59:1340-50.
PMID: 30997931.</td>
<td>3

PM: A
IM: A</td>
<td>110 patients with haematological disorders were treated with voriconazole for possible, probable or proven invasive fungal infection. All patients were treated with voriconazole 200 mg twice daily, either orally (80.5%) or intravenously (19.5%).
Steady state voriconazole trough concentrations were determined. A mean of 2.2 samples per patient was analysed. The mean trough concentration was not statistically different between the oral and intravenous route.
10.4% of voriconazole trough concentrations were subtherapeutic (< 0.5 µg/mL) and 16% were supratherapeutic (> 5 µg/mL).
Comedication with strong inducers and inhibitors of CYP enzymes was excluded, but moderate or weak inducers and inhibitors were not.

Genotyping:
- 38x NM
- 50x IM
- 22x PM

Results:
<table>
<tr><td colspan="4">Results compared to NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>median voriconazole concentration</td><td>x 3.07 (S)</td><td>x 2.14 (S)</td><td>1.4 µg/mL</td></tr>
<tr><td></td><td colspan="2">Multiple linear regression analysis showed PM and IM to be independent predictors of voriconazole trough concentration (S).
Together with age, plasma γ-glutamyl transferase, interleukin-6 levels, and proton pump inhibitor coadministration, they explained 29% of the variation in the vorico-</td><td></td></tr>
</table>
</td>
<td>Authors’ conclusions: “Furthermore, patient age, gamma-glutamyl transferase, IL-6, proton pump inhibitor coadministration, and cytochrome P450 2C19 polymorphism partially predicted the voriconazole C_{min}.”

Median trough concentration$_{steady\ state}$ at a dose of 400 mg per day versus NM:
IM: 214%
PM: 307%</td>
</tr>
</table>

ref. 10, continuation		nazole trough concentration. Note: Genotyping was for *2 and *3. These are the most important gene variants in this Chinese population.	
ref. 11 Sienkiewicz B et al. Influence of CYP-2C19 genotypes on the occurrence of adverse drug reactions of voriconazole among hematological patients after allo-HSCT. Pathol Oncol Res 2018;24:541-5. PMID: 28685218. **ref. 11, continuation**	3 UM: AA IM: AA	30 allogeneic hematopoietic stem cell transplantation patients were prophylactically treated with voriconazole (doses not reported). Voriconazole prophylaxis failed in two cases (6.7% of patients), where an invasive pulmonary aspergillosis occurred. Adverse events on the day before start of voriconazole and the first 20 treatment days were examined. 77% of patients suffered from at least one side effect during therapy. The presented complications were temporary and had no impact on the dose regimen nor the conducted pharmacotherapy. Most frequent adverse drug reactions were gastrointestinal disturbances (50% of patients), nervous system disorders (37% of patients) and skin disorders (23% of patients). Comedication with effect on CYP2C19 and voriconazole metabolism was not excluded. Genotyping: - 3x UM - 12x NM (4x *1/*1, 8x *1/*17) - 15x IM (5x *1/*2, 10x *2/*17) Results: Effect on % of patients with adverse events: CYP2C19 genotype: NS The % of patients with adverse events was numerically higher for IM. The authors postulate that the absence of a significant effect is due to the limited number of patients. Note: Genotyping was for *2 and *17. These are the most important gene variants in this Polish population.	Authors' conclusions: "Patients with at least one loss of function allele (*2) were more likely to experience adverse drug reactions than those, with different genotypes. Due to the limited number of patients the result could not be proven with a statistical significance. Previous determination of CYP2C19 genotype may be a useful tool for prevention of adverse drug reactions during voriconazole prophylaxis among patients after allogeneic hematopoietic stem cell transplantation."
ref. 12 Hamadeh IS et al. Impact of the CYP-2C19 genotype on voriconazole exposure in adults with invasive fungal infections. Pharmacogenet Genomics 2017;27:190-6. PMID: 28306618.	3	70 patients with proven or probable invasive fungal infection were treated with voriconazole. 63% of patients received voriconazole intravenously, 37% orally. All patients started on a loading dose of 6 mg/kg every 12 hours for the first 24 hours, followed by a maintenance dose of 4 mg/kg every 12 hours. If necessary, dose was adjusted based on voriconazole concentration thereafter. 30% of patients had a subtherapeutic first voriconazole concentration (< 2 µg/mL) and 20% a supratherapeutic first voriconazole concentration (> 6 µg/mL). Steady state voriconazole trough concentrations were determined. None of the patients used CYP2C19 inhibitors or inducers. Of the original group of 81 patients with proven or probable invasive fungal infection starting voriconazole, 11 (13.6%) discontinued voriconazole before sampling for plasma concentration measurement on day 5-7 day of treatment. Reasons for discontinuation and genotypes of patients were not reported. A power calculation showed that the inclusion of at least 70 patients, with 14 expected to have the *1/*17 or UM genotype based on reported phenotype frequencies, provides 80% power to detect a 30% difference in the prevalence of	Authors' conclusions: "Our findings indicate that adults with the CYP2C19 RM or UM phenotype are more likely to have subtherapeutic concentrations with weight-based voriconazole dosing. These results corroborate previous findings in children and support potential clinical utility of CYP-2C19 genotype-guided voriconazole dosing to avoid underexposure in RMs and UMs."

<table>
<tr>
<td>ref. 12, continuation</td>
<td>IM+PM: AA
UM: A</td>
<td>
subtherapeutic trough plasma concentrations (< 2 µg/mL) between *1/*17+UM and *1/*1+IM+PM.

Genotyping:
- 3x UM
- 24x *1/*17
- 28x *1/*1
- 14x IM
- 1x PM

Results:
<table>
<tr><td colspan="5">Results compared to *1/*1 or *1/*1+IM+PM:</td></tr>
<tr><td></td><td>IM+PM</td><td>*1/*17</td><td>UM</td><td>value for *1/*1 or *1/*1+ IM+PM</td></tr>
<tr><td rowspan="3">first voriconazole concentration</td><td>x 0.97 (NS)</td><td>x 0.70 (trend: p = 0.05) (NS)</td><td>x 0.32 (S)</td><td rowspan="3">*1/*1: 4.27 µg/mL</td></tr>
<tr><td colspan="3">The first voriconazole concentration for UM is 0.37x that for NM (3.67 µg/mL).</td></tr>
<tr><td colspan="3">Also compared to IM+PM, the difference was significant for UM, but not for *1/*17 (p = 0.10).</td></tr>
<tr><td rowspan="2">% of patients with a subtherapeutic first voriconazole concentration (< 2 µg/mL)</td><td rowspan="2"></td><td>x 2.8 (S)</td><td>x 6.2 (S)</td><td rowspan="2">*1/*1+ IM+PM: 16.2%</td></tr>
<tr><td colspan="2">Multiple logistic regression analysis showed *1/*17+UM to be a predictor of subtherapeutic first voriconazole concentrations (< 2 µg/mL) (OR = 5.6; 95% CI: 1.6-19.2). The only other predictor found was weight ≤ 70 kg.</td></tr>
<tr><td>% of patients with a first voriconazole concentration < 1 µg/mL</td><td></td><td colspan="2">x 3.9 (S)</td><td>*1/*1+ IM+PM: 7%</td></tr>
<tr><td>% of patients with a supratherapeutic first voriconazole concentration (> 6 µg/mL)</td><td>x 0.37 (NS)</td><td colspan="2">x 0.21 (S)</td><td>*1/*1: 35.7%</td></tr>
<tr><td colspan="5">Effect of 25% dose increase in UM and *1/*17:
Voriconazole was either discontinued or switched to an alternative antifungal agent in 79% of *1/*17+UM with a subtherapeutic first voriconazole trough concentration. In two UM and one *1/*17, the dose was increased by 25% to 5 mg/kg every 12 hours. This resulted in therapeutic trough concentrations in one UM (2.4 µg/mL) and the</td></tr>
</table>
</td>
<td>Trough concentration$_{steady\ state}$ at a dose of 8 mg/kg per day versus NM:
UM: 37%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 12, continuation</td>
<td></td>
<td>
<table><tr><td>*1/*17 (2.9 µg/mL), and a concentration of 1.85 µg/mL in the other UM. No hepatotoxicity or other adverse effects were observed following dose increase.</td></tr></table>

Note: Genotyping was for *2, *3, and *17. These are the most important gene variants in this population from the USA. *3 was not found in this patient group.
</td>
<td></td>
</tr>
<tr>
<td>ref. 13
Li X et al.
Effect of cytochrome P450 2C19 polymorphisms on the clinical outcomes of voriconazole: a systematic review and meta-analysis.
Eur J Clin Pharmacol
2016;72:1185-93.
PubMed PMID: 27388292.</td>
<td>4

3
PM: AA#</td>
<td>A meta-analysis of 10 studies including a total of 598 patients on voriconazole, of which 262 IM, 67 PM and 10 patients with a *17 allele. Patients with a *17 allele were not included in the meta-analysis. In these studies, either the CYP2C19 genotype or phenotype was determined. The steady-state trough concentrations were measured in these studies. The definitions of a successful treatment varied between the studies. Neurotoxicity was defined as encephalopathy, auditory or visual hallucinations, confusion or epileptic seizures. If studies only reported median results, these were converted to the estimated average using the method of Hozo 2005.The included studies scored 8-10 of the maximum of 10 points on the quality checklist derived from the Strengthening the Reporting of Genetic Association (STREGA) recommendations for reports on genetic association studies.
The treatment success was determined in 4 studies involving a total of 292 patients, of which 149 IM and 33 PM. Of these studies, Wang 2014 and Kim 2013 have also been included separately in this risk analysis.
For all side effects, there were 6 studies with a total of 348 patients, of which 176 IM and 49 PM. For hepatotoxicity, there were 4 studies with a total of 282 patients, including 136 IM and 37 PM, and for neurotoxicity there were 3 studies with a total of 141 patients, including 74 IM and 20 PM.
For voriconazole trough concentration, there were 7 studies with a total of 517 patients, of which 216 IM and 65 PM. Of these studies, 5 (Chuwongwattana 2016, Wang 2014, Zonios 2014, Kim 2013 and Brüggeman 2010) have also been included separately in this risk analysis.
For the maintenance dose, there were 3 studies with a total of 83 patients, of which 59 IM. Of these studies, Matsumoto 2009 and Berge 2011 have also been included separately in this risk analysis.
A random effects model was used for all meta-analyses, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias analysis was assessed with funnel plots, but only for the comparisons of the trough concentrations and all side effects. Indications for publication bias were present for both comparisons. Publication bias was not examined for the other comparisons due to the low number of studies.

Results:
<table>
<tr><td colspan="3">Relative risks and differences versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td></tr>
<tr><td>Treatment success</td><td>RR = 1.31; 95% CI: 1.04-1.67 (S)</td><td>NS</td></tr>
<tr><td>All side effects</td><td>NS</td><td>NS</td></tr>
</table>
</td>
<td>Authors' conclusions: "Patients with CYP2C19 PM phenotype were associated with increased treatment success rate and trough concentrations as compared with those with NM phenotype. There was no significant association between CYP2C19 polymorphisms and either daily maintenance dose or adverse outcomes of voriconazole. However, large-scale, high-quality trials are still needed to confirm these findings."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 13, continuation</td>
<td>IM: A</td>
<td>
<table>
<tr><td>Hepatotoxicity</td><td>NS</td><td>NS</td></tr>
<tr><td>Neurotoxicity</td><td>NS</td><td>NS</td></tr>
<tr><td>Difference in voriconazole trough concentration (mg/L)</td><td>+ 1.22 (S)</td><td>+ 0.61 (S)</td></tr>
<tr><td>Difference in maintenance dose (mg/kg per day)</td><td></td><td>NS</td></tr>
<tr><td colspan="3">There was heterogeneity between the studies for:
- the voriconazole trough concentration and PM. Removal of Chuwongwattana 2016 from the meta-analysis resulted in the disappearance of heterogeneity without a change in the result (average difference = 1.32 (S)).</td></tr>
<tr><td colspan="3">Indications of publication bias were present for:
- the voriconazole trough concentration and PM and IM
- all side effects and PM and IM
The publication bias was not examined for the other comparisons due to the low number of studies.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 14
Wang Y et al.
Risk factors for voriconazole-associated hepatotoxicity in patients in the intensive care unit.
Pharmacotherapy 2016;36:757-65.
PubMed PMID: 27284960.</td>
<td>3

IM: AA
PM: A</td>
<td>
63 patients who were admitted to the intensive care unit for more than 3 days were treated with voriconazole. The dose was determined based on the SmPC and the median dose was 6.7-7 mg/kg per day for a median of 11-13 days. Relevant co-medication was not excluded. Co-medication with the largest difference in use between patients with and without hepatotoxicity had no significant effect on this side effect, but a trend was found for cefoperazone-sulbactam. Hepatotoxicity was defined as an increase of 2 grades on the National Cancer Institute Common Terminology Criteria for Adverse Events after start of treatment with voriconazole. 12 patients developed hepatotoxicity (after a median of 8 days of treatment).
Trough concentrations were determined in steady state (on day 2 or later for patients who received a loading dose, or day 7 or later for patients who did not receive a loading dose; median of 6 days after the first dose).

Genotyping:
- 31x NM
- 24x IM
- 8x PM

Results:
<table>
<tr><td colspan="3">PM versus IM versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td></tr>
<tr><td>Hepatotoxicity</td><td colspan="2">Increase in the risk with the number of inactive gene variants in univariate analysis (HR = 2.53; 95% CI: 1.22-5.25) (S), but not in multivariate analysis (NS)</td></tr>
<tr><td>Voriconazole trough concentration</td><td>elevated (S)</td><td></td></tr>
<tr><td colspan="3">In multivariate analysis, the voriconazole trough concentration was the only independent predictive variable for hepatotoxicity. The authors indicate that the relatively low number of PMs in this study could be a possible cause for the absence of a significant effect of the genotype on hepatotoxicity.</td></tr>
</table>
</td>
<td>Authors' conclusions: "In the present study, PMs indeed had significantly higher trough voriconazole plasma concentrations than either IMs or NMs, which is consistent with the CYP2C19 genotype prediction. However, similar to the findings of others, the current study found no significant relationship between voriconazole hepatotoxicity and CYP2C19 genotypes in critically ill patients."</td>
</tr>
</table>

<table>
<tr><td>ref. 14, continuation</td><td></td><td>Note: Genotyping was performed for *2, *3 and *17. *17 was not found in this Chinese patient group.</td><td></td></tr>
<tr><td>ref. 15
Williams K et al.
Association of CYP-2C19 *17/*17 genotype with the risk of voriconazole-associated squamous cell carcinoma.
JAMA Dermatol 2016;152:719-20.
PubMed PMID: 26982740.</td><td>3

(*1/*17+ UM): AA</td><td>Part of a group of 177 lung transplant patients were treated with voriconazole.
Relevant co-medication was not excluded.
Cumulative voriconazole exposure was measured per 30 days with a dose of 200 mg 2x daily.

Genotyping:
- 11x UM
- 45x *1/*17
- 63x *1/*1
- 47x IM
- 5x PM

Results:
<table>
<tr><td colspan="2">(*1/*17 + UM) versus (*1/*1 + PM + IM):</td></tr>
<tr><td>Cutaneous squamous cell carcinoma</td><td>Increase in the risk in univariate analysis (HR = 1.74; 95% CI: 1.06-2.84) and bivariate analysis with correction for exposure to voriconazole (HR = 1.76; 95% BI: 1.07-2.89) (S).
Trend for an increase in the risk in bivariate analysis with correction for the cumulative exposure to voriconazole (HR = 1.61; p = 0.053) and with correction for exposure to voriconazole, male gender, Caucasian race and age over 50 years at transplant (HR = 1.52; p = 0.09) (NS).
No significant effect with correction for the cumulative exposure to voriconazole, male gender, Caucasian race and age over 50 years at transplant (NS).</td></tr>
<tr><td colspan="2">The significant effect of exposure to voriconazole in univariate analysis (HR = 1.91; 95% CI: 1.11-3.27) disappeared after correction for the presence of the *17 allele. These and the other corrections had no effect on the significant effect of the cumulative exposure to voriconazole, but this effect was small (HR = 1.02; 95% CI: 1.01-1.04).</td></tr>
</table>
Note: Genotyping was performed for *2, *3 and *17.</td><td>Authors' conclusions: "Our findings suggest that the ultrarapid metabolic CYP2C19 *17 allele is associated with squamous cell carcinoma (SCC) risk and modifies the association between exposure to voriconazole and SCC. Further studies with a larger sample size are required to investigate whether these findings are statistically significant for cumulative dose exposure and in models adjusted for additional SCC risk factors including sex, race, and age at transplantation."</td></tr>
<tr><td>ref. 16
Chuwongwattana S et al.
A prospective observational study of CYP2C19 polymorphisms and voriconazole plasma level in adult Thai patients with invasive aspergillosis.
Drug Metab Pharmacokinet 2016;31:117-22.
PubMed PMID: 26861072.</td><td>3</td><td>115 patients were treated with voriconazole (400-500 mg/day; either intravenous with loading doses of 6 mg/kg followed by a maintenance dose of 4 mg/kg 2x daily, or oral with 200-250 mg 2x daily). Relevant co-medication was not excluded.
An average of 2.45 trough concentrations per patient were determined in steady state (minimum of 7 days after start of therapy).

Genotyping:
- 59x NM
- 42x IM
- 14x PM

Results:
<table>
<tr><td colspan="4">PM versus IM versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>Value</td></tr>
</table></td><td>Authors' conclusions: "An association between CYP2C19 variant alleles and high voriconazole plasma level was identified. Therefore, determining the CYP2C19 genotype before initiation of voriconazole treatment may be useful in optimizing the dosing regimen in Thai patients with invasive fungal infections."</td></tr>
</table>

<table>
<tr>
<td>ref. 16, continuation</td>
<td>PM: A
IM: AA</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>for NM</td></tr>
<tr><td rowspan="2">Median voriconazole trough concentration</td><td>x 1.29 (S)</td><td>x 1.27 (NS)</td><td>1.470 µg/mL</td></tr>
<tr><td colspan="3">There was a trend for PM versus IM versus NM (NS, p = 0.085).</td></tr>
<tr><td>% of supratherapeutic trough concentrations (> 4 µg/mL)</td><td>x 2.06</td><td>x 1.87</td><td>11%</td></tr>
<tr><td>% therapeutic trough concentrations (1-4 µg/mL)</td><td>x 1.18</td><td>x 0.95</td><td>53%</td></tr>
<tr><td>% of subtherapeutic trough concentrations (< 1 µg/mL)</td><td>x 0.41</td><td>x 0.82</td><td>36%</td></tr>
<tr><td></td><td colspan="3">The distribution over the various trough concentration groups differed between NM and (IM + PM) (S), whilst there was a trend for PM versus IM versus NM (p = 0.076; NS)</td></tr>
<tr><td colspan="4">The variation in the trough concentration within each of the genotype groups was greater than a factor of 3 and therefore also much larger than the difference between the genotype groups.</td></tr>
</table>

Note: Genotyping was performed for *2, *3 and *17. *17 was not found in this Thai patient group.
</td>
<td>Median trough concentration$_{steady\ state}$ at a dose of 400-500 mg/day versus NM:
IM: 127%
PM: 129%</td>
</tr>
<tr>
<td>ref. 17
Teusink A et al. Genotype-directed dosing leads to optimized voriconazole levels in pediatric patients receiving hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2016;22:482-6. PubMed PMID: 26616742.</td>
<td>3</td>
<td>25 patients of median age 7 years (0.8-23 years) received non-genotype-guided prophylaxis with voriconazole. Next, 20 patients of median age 10.9 years (0.8-26.4 years) received genotype-guided prophylaxis.
Non-genotype-guided prophylaxis started at a dose of 5 mg/kg 2x daily. Voriconazole trough concentrations were determined after 8 doses, as this was calculated as the time at which most patients achieved steady state. The dose was adjusted until the trough concentration was within the therapeutic range (1-5.5 µg/mL). If the trough concentration was lower than 1 µg/mL, the dose was increased by 25% and the trough concentration was determined again after 8 doses. If the trough concentration was higher than 5.5 µg/mL, then two doses were skipped and this was followed by half of the previous dose.
In the case of genotype-guided prophylaxis, the dose started at 7 mg/kg 2x daily for NM and UM and 6 mg/kg 2x daily for IM and patients with unknown genotype. For PM, the planned initial dose was the normal initial dose of 5 mg/kg 2x daily. Voriconazole trough concentrations were determined after 8 doses. The dose was adjusted until the trough concentration was within the therapeutic range (1-5.5 µg/mL). If the trough concentration was lower than the detection limit (0.1 µg/mL), the dose was increased by 50% and if the trough concentration was 0.1-1 µg/mL, the dose was increased by 25%. The new trough concentration was determined again after 8 doses. If the trough concentration was higher than 5.5 µg/mL, then two doses were skipped and this was followed by 50-75% of the previous dose.
For both genotype-guided and non-genotype-guided prophylaxis, the trough concentration was checked weekly for 1 month after achieving the therapeutic range and then every 2 weeks until end of treatment. Extra trough concen-</td>
<td>Authors' conclusions: "Overall, the median time to reach the target concentration with genotype-guided dosing was 6.5 days compared with a median time of 29 days when all patients were started on the same dose regardless of CYP-2C19 genotype. Our data show that traditional voriconazole dosing does not lead to timely achievement of target levels for fungal prophylaxis. However, a genotype-guided dosing algorithm allows patients to reach the voriconazole target range significantly sooner, providing better prophylaxis against fungal infections in the immediate post-transplant period."</td>
</tr>
</table>

<table>
<tr>
<td>ref. 17, continuation</td>
<td>Genotype-guided versus not genotype-guided therapy: all patients: A
*1/*17: AA
*1/*1: AA
IM: AA

*1/*17: AA
IM: AA
PM: AA</td>
<td>
tration determinations were performed if there were indications of voriconazole toxicity or a fungal infection.
Relevant co-medication was not excluded.
Three patients in the non-genotype-guided study never achieved the therapeutic range. Considering the data about the doses required to achieve the therapeutic range, these patients must have had the NM genotype.

Genotyping:
Non-genotype-guided group
- 2x *1/*17
- 17x *1/*1
- 3x IM
- 2x PM
- 1x unknown

Genotype-guided group
- 1x *1/*17
- 10x *1/*1
- 7x IM
- 2x unknown

Results:
<table>
<tr><td colspan="4">Genotype-guided versus non-genotype-guided prophylaxis:</td></tr>
<tr><td colspan="2"></td><td></td><td>Value for non-genotype-guided prophylaxis</td></tr>
<tr><td rowspan="5">Median time required to achieve therapeutic trough concentrations (1-5.5 µg/mL)</td><td>total</td><td>x 0.22 (S)</td><td>29 days</td></tr>
<tr><td>*1/*17</td><td>x 0.42 (NS)</td><td>22 days</td></tr>
<tr><td>*1/*1</td><td>x 0.19 (NS)</td><td>34 days</td></tr>
<tr><td>IM</td><td>x 0.07 (NS)</td><td>56 days</td></tr>
<tr><td>PM</td><td>-</td><td>11 days</td></tr>
<tr><td colspan="2">The median dose required to achieve therapeutic trough concentrations (1-5.5 µg/mL)</td><td>NS</td><td>11.6 mg/kg per day</td></tr>
<tr><td colspan="2">% of patients with a supra-therapeutic trough concentration (> 5.5 µg/mL)</td><td>x 0 (NS)</td><td>8%</td></tr>
<tr><td colspan="2">% of patients with an infection with a voriconazole-sensitive fungus</td><td>x 0 (NS)</td><td>4%</td></tr>
<tr><td colspan="2">% of patients with elevated liver enzymes</td><td>x 0.25 (NS)</td><td>20%</td></tr>
<tr><td colspan="2">% of patients that stopped voriconazole due to toxicity</td><td>x 0 (NS)</td><td>8%</td></tr>
<tr><td colspan="2">% of patients with visual and neurological changes</td><td>x 0 (NS)</td><td>4%</td></tr>
<tr><td colspan="4">The difference between the genotype groups in the median time required to achieve therapeutic trough concentrations for non-genotype-guided prophylaxis was non-significant (NS). This was probably caused by the low number of patients per group.</td></tr>
</table>

<table>
<tr><td colspan="2">The median dose required to achieve therapeutic trough concentrations (1-5.5 µg/mL) versus *1/*1 (5.7 mg/kg 2x daily):</td></tr>
<tr><td>*1/*17</td><td>x 1.22 (NS)</td></tr>
<tr><td>IM</td><td>x 1.05 (NS)</td></tr>
<tr><td>PM</td><td>x 1.07 (NS)</td></tr>
<tr><td colspan="2">The difference in median required dose between the genotype groups is small in comparison to the difference of a factor of 6.7 between the patient with the lowest and</td></tr>
</table>
</td>
<td>The median dose required to achieve therapeutic trough concentrations (1-5.5 µg/mL) versus *1/*1:
IM: 105%
PM: 107%</td>
</tr>
</table>

ref. 17, continuation		highest doses in the non-genotype-guided group (5.4 and 36.3 mg/kg per day respectively). Note 1: According to the Kinderformularium, the dose used in the non-genotype-guided treatment is too low for children aged 2-15 years with a body weight lower than 50 kg. An intravenous initial dose of 9 mg/kg 2x daily is recommended for this group, followed by an intravenous dose of 8 mg/kg 2x daily and finally an oral dose of 9 mg/kg 2x daily. For older and heavier children, an intravenous initial dose of 6 mg/kg 2x daily and a maintenance dose of 4 mg/kg 2x daily are recommended, or an oral initial dose of 400 mg 2x daily and a maintenance dose of 200 mg 2x daily. Note 2: Genotyping was performed for *2-*8 and *17.	
ref. 18 Lamoureux F et al. Impact of CYP2C19 genetic polymorphisms on voriconazole dosing and exposure in adult patients with invasive fungal infections. Int J Antimicrob Agents 2016;47:124-31. PubMed PMID: 26775563.	4	35 patients were treated with oral voriconazole. Patients received voriconazole 200 mg 2x daily, with or without prior loading doses of 400 mg every 12 hours for 24 hours. The trough concentration was measured in steady state (after 2 days for patients who received loading doses and after 6 days for patients who did not receive loading doses). Patients who received intravenous voriconazole were only included if they had been switched to oral voriconazole at least 2 days before determination of the trough concentration. In 55% of the patients, the peak plasma concentration (2 hours after the dose) was also determined and therefore also the absorption. In 4.5% of patients, the plasma concentration was also determined 2, 4, 6, 8 and 10 hours after the dose and therefore also the AUC, because it was difficult to achieve therapeutic concentrations in these patients. The doctors decided about dose adjustment based on the determined trough concentration and the CYP2C19 genotype. The target value for the trough concentration was 1-5 µg/mL. In general, the dose was increased or reduced by 50-100 mg or 0.5-1 mg/kg 2x daily for trough concentrations < 1 µg/mL or > 5 µg/mL. Termination of treatment was recommended for patients with a trough concentration > 5 µg/mL and voriconazole-associated side effects. Part of the genotyping was performed prior to the treatment and part was performed in response to extreme trough concentrations. Relevant co-medication was not excluded, but correction was performed in multivariate analysis for co-medication with CYP inducers and for co-medication with CYP inhibitors. None of the patients used strong CYP inducers or inhibitors. Two patients were not included in the study, because they had genotype *2/*17. Genotyping: - 4x UM - 13x *1/*17 - 11x *1/*1 - 6x IM (only *1/*2) - 1x PM Results: Results versus *1/*1 (↑ = increase, ↓ = decrease):	Authors' conclusions: "Indices of exposure for CYP2C19*2 carriers were in line with the functional effect of this polymorphism compared with CYP2C19*1/*1 individuals, however comparisons of doses required to achieve target concentrations were not statistically different. The CYP2C19 *17 allele predicted both exposure and dose required to achieve effective and non-toxic concentrations. CYP2C19 genotyping appears useful to guide voriconazole initial dosing when coupled with TDM and to explain subtherapeutic concentrations frequently observed in clinical practice."

<table>
<tr>
<td>ref. 18, continuation</td>
<td>*1/*17: A
IM: A
PM: AA

UM: A</td>
<td>
<table>
<tr><td></td><td>UM</td><td>*1/*17</td><td>IM</td><td>PM</td><td>Value for *1/*1</td></tr>
<tr><td>Trough concentration</td><td>↓ (NS, trend, p = 0.082)</td><td>↓ (S)</td><td>↑ (S)</td><td>↑</td><td>approx. 3.1 µg/mL</td></tr>
<tr><td></td><td colspan="4">UM and *1/*17 were significantly more likely to have subtherapeutic trough concentrations (S) and no supratherapeutic trough concentrations, so fewer supratherapeutic trough concentrations than *1/*1.</td><td></td></tr>
<tr><td>Daily dose and weight-corrected trough concentration</td><td>x 0.15 (S)</td><td>x 0.23 (S)</td><td>x 0.86 (NS)</td><td>x 1.39</td><td>0.76 µg.kg/mL.mg</td></tr>
<tr><td>The dose required to achieve the therapeutic range</td><td>x 2.63 (S)</td><td>x 1.53 (S)</td><td>x 1.32 (NS)</td><td>x 0.70</td><td>5.15 mg/kg per day</td></tr>
<tr><td colspan="6">No side effects, such as abnormal facial functioning or altered liver function, occurred in this patient group.</td></tr>
<tr><td colspan="6">The authors suggested initial doses of 2.5, 4 and 6 mg/kg 2x daily for *1/*1, *1/*17 and UM respectively. For UM, this is lower than the determined required dose of 6.75 mg/kg 2x daily.</td></tr>
</table>

Note: Genotyping was performed for *2 and *17. These are the most important gene variants in this Caucasian patient group.
</td>
<td>The dose required to achieve therapeutic trough concentrations (1-5 µg/mL) versus NM:
UM: 204%
IM: 103%
PM: 54%</td>
</tr>
<tr>
<td>ref. 19
Weigel JD et al. Gain-of-function single nucleotide variants of the CYP 2C19 gene (CYP 2C19*17) can identify subtherapeutic voriconazole concentrations in critically ill patients: a case series. Intensive Care Med 2015;41:2013-4. PubMed PMID: 26239729.</td>
<td>3

*17: AA</td>
<td>6 patients in the intensive care unit were treated with intravenous voriconazole (6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily). Therapeutic drug monitoring was performed, with the aim of achieving a therapeutic range of 1.7-5.0 µg/mL. The first trough concentration was determined a median of 4 days (1-8 days) after the start of treatment, the second and third trough concentrations were determined a median of 3 days (1-10 days) and median of 4 days (1-16 days) respectively after the previous trough concentration determination. Trough concentrations were determined in steady state.
Relevant co-medication was not excluded.

Genotyping:
- 3x *1/*17
- 3x *1/*1

Results:
<table>
<tr><td colspan="3">*1/*17 versus *1/*1:</td></tr>
<tr><td></td><td></td><td>Value for *1/*1</td></tr>
<tr><td>% of the first 3 trough concentrations that was subtherapeutic (< 1.7 µg/mL)</td><td>x 2.33 (NS)</td><td>33%</td></tr>
</table>
</td>
<td>Authors' conclusions: "The CYP2C19*1/*17 genotype is associated with low voriconazole plasma trough concentrations in ICU patients. Pre-emptive genotyping of CYP-2C19 might identify patients at risk of underexposure to voriconazole. Prospective studies are warranted to evaluate the added benefit of pre-emptive genotyping for pharmacokinetics and clinical outcomes in critically ill patients."</td>
</tr>
</table>

<table>
<tr><td>ref. 19, continuation</td><td></td><td>
<table>
<tr><td colspan="2">% of the first 3 trough concentrations that was < 1.0 µg/mL</td><td>x 3.00 (NS)</td><td>22%</td></tr>
<tr><td rowspan="3">Median dose-corrected trough concentration (µg.kg/mL.mg)</td><td>1st trough concentration</td><td>x 0.31 (NS)</td><td>0.29</td></tr>
<tr><td>2nd trough concentration</td><td>x 0.13 (NS)</td><td>0.30</td></tr>
<tr><td>3rd trough concentration</td><td>x 0.12 (NS)</td><td>0.25</td></tr>
<tr><td colspan="4">For *1/*17, 78% of the trough concentrations were lower than 1.7 µg/mL and 67% were lower than 1.0 µg/mL. Percentages higher than 67% mean that a proportion of the patients will not have achieved the desired trough concentration even after two dose increases (median of 11 days).</td></tr>
</table>
Note: Genotyping was only performed for *17.
</td><td></td></tr>
<tr><td>ref. 20
Chawla PK et al. Correlation of CYP-2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians.
Int J Clin Pharm 2015;37:925-30.
PubMed PMID: 26024717.</td><td>3

UM: 1AA

*1/*17:
AA
IM: AA
PM: A</td><td>37 patients were treated with 200 mg voriconazole 2x daily. Trough concentrations were determined after at least 4 days of treatment. Relevant co-medication was not excluded.
1 UM, who was not included in the study, achieved trough concentrations in the therapeutic range (2-6 µg/mL) with a standard weight-based dose.

Genotyping:
- 10x *1/*17
- 8x *1/*1
- 15x IM
- 4x PM

Results:
<table>
<tr><td colspan="2">Median trough concentration at a dose of 200 mg 2x daily versus *1/*1 (2.5 µg/mL) (trough concentrations can be read from the figure):</td></tr>
<tr><td>*1/*17</td><td>x 0.96 (NS)</td></tr>
<tr><td>IM</td><td>x 1.1 (NS)</td></tr>
<tr><td>PM</td><td>x 1.7 (S)</td></tr>
</table>
Note: Genotyping was performed for *2, *3 and *17.</td><td>Authors' conclusions: "Plasma voriconazole levels are influenced by CYP2C19 variants, drug interactions and clinical condition of the patient. Genotype assessment at initiation of therapy followed by drug monitoring would help optimizing therapeutic efficacy and minimizing toxicity."

Median trough concentration_{steady state} versus *1/*1:
IM: 110%
PM: 170%</td></tr>
<tr><td>ref. 21
Yamada T et al. Saturated metabolism of voriconazole N-oxidation resulting in nonlinearity of pharmacokinetics of voriconazole at clinical doses.
Biol Pharm Bull 2015;38:1496-503.
PubMed PMID: 26424015.</td><td>3

IM: AA
PM: AA</td><td>47 patients were treated with oral or intravenous voriconazole (median 200 mg 2x daily). Trough concentrations were determined after at least 4 days of treatment. Co-medication with rifampicin, ritonavir, carbamazepine and long-acting barbiturates was excluded, other relevant co-medication was not.

Genotyping:
- 16x NM
- 25x IM
- 6x PM

Results:
<table>
<tr><td colspan="3">Median dose-corrected and weight-corrected trough concentration of voriconazole versus NM (0.51 µg.kg/mL.mg):</td></tr>
<tr><td>IM</td><td>x 1.7</td><td rowspan="2">NS for the trend PM versus IM versus NM</td></tr>
<tr><td>PM</td><td>x 1.5</td></tr>
</table>
Note: Genotyping was performed for *2 and *3. These are the most important gene variants in this Japanese patient group.</td><td>Authors' conclusions: "No significant differences in the trough plasma concentrations of voriconazole and N-oxide between the CYP2C19 genotypes were observed. Saturated metabolism of voriconazole N-oxidation rather than CYP2C19 genotypes contributed to the nonlinear pharmacokinetics."

Median trough concentration_{steady state} versus NM:
IM: 170%
PM: 150%</td></tr>
</table>

<table>
<tr>
<td>ref. 22
Mori M et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese pediatric patients. Antimicrob Agents Chemother 2015;59:1004-13. PubMed PMID: 25451051.</td>
<td>3

IM: AA
PM: AA</td>
<td>21 patients aged 2-15 years were treated prophylactically with voriconazole. For children up to 12 years and those aged 12-15 years weighing less than 50 kg, the dose used was an intravenous loading dose of 9 mg/kg 2x daily on day 1, followed by an intravenous dose of 8 mg/kg 2x daily on days 2-7 and finally an oral dose of 9 mg/kg (to a maximum of 350 mg) 2x daily on days 8-14. For children aged 12-15 years and weighing 50 kg or more, the dose used was an intravenous loading dose of 6 mg/kg 2x daily on day 1, followed by an intravenous dose of 4 mg/kg 2x daily on days 2-7 and finally an oral dose of 200 mg/kg 2x daily on days 8-14. If necessary, the intravenous treatment could be extended to a maximum of 20 days, before switching to oral treatment. If necessary, the total voriconazole treatment could be extended to 30 days. Both patients who weighed 50 kg or more and who therefore received the lower dose were NM. Follow-up was 30 days after the last dose. Trough concentrations were determined on the 7th day of the intravenous and oral treatment (steady state). Plasma concentrations to determine the AUC were determined on day 7 of the intravenous and oral treatment. There were insufficient concentration data available for 1 NM aged 11 years. There were insufficient concentration data available for the oral dose given to 1 NM weighing 50 kg or more and 1 NM lighter than 50 kg. Co-medication with CYP-450 inhibitors and inducers and with other medicines that should not be used according to the SmPC for voriconazole were excluded, but corticosteroids and - for 1 patient omeprazole on days 1 and 2 - were not.

Genotyping:
- 9x NM
- 10x IM
- 2x PM

Results:
<table>
<tr><td colspan="5">Results versus NM:</td></tr>
<tr><td></td><td></td><td>PM</td><td>IM</td><td>Value for NM</td></tr>
<tr><td rowspan="2">intravenous</td><td>AUC_{0-12h}</td><td>x 3.6 (NS)</td><td>x 1.6 (NS)</td><td>36.0 µg.hour/mL</td></tr>
<tr><td>trough concentration</td><td>x 4.3 (NS)</td><td>x 1.4 (NS)</td><td>1.83 µg/mL</td></tr>
<tr><td rowspan="2">oral</td><td>AUC_{0-12h}</td><td>x 3.2 (NS)</td><td>x 1.6 (NS)</td><td>31.2 µg.hour/mL</td></tr>
<tr><td>trough concentration</td><td>x 4.4 (NS)</td><td>x 1.6 (NS)</td><td>1.17 µg/mL</td></tr>
<tr><td colspan="2">side effects</td><td colspan="2">NS (no difference between the groups)</td><td></td></tr>
<tr><td colspan="5">For PM, after both intravenous and oral doses, the average trough concentration was higher than 5 µg/mL (7.82 and 5.13 µg/mL respectively).</td></tr>
<tr><td colspan="5">No very severe side effects occurred and there were no deaths. In the total group, side effects occurred in 85.7% of the patients and these were voriconazole-related in 57.1%. One of the PMs had no side effects and the other had no voriconazole-related side effects. Both patients who stopped treatment due to the voriconazole-related side effect of “liver function abnormalities” were NM.</td></tr>
</table>
</td>
<td>Authors’ conclusions: “The exposures in the 2 cytochrome P450 2C19 poor metabolizers were among the highest. Voriconazole was well tolerated. ….. Although the average exposure values in the heterozygous normal metabolizers (HNM group) were higher than those in the NM group, there was a substantial overlap in the voriconazole exposures between these 2 groups.”

Trough concentration$_{steady\ state}$ versus NM:
IM: 150%
PM: 430%</td>
</tr>
</table>

<table>
<tr><td>ref. 22, continuation</td><td></td><td>The results of this study did not concur with a therapeutic lower limit of 1 µg/mL and an upper limit of 4 µg/mL.

Note 1: Genotyping was performed for *2-*5 and *17.

Note 2: The dosing schedules used correspond to the dosing schedules listed in the Kinderformularium.</td><td></td></tr>
<tr><td>ref. 23
Wang T et al.
Efficacy and safety of voriconazole and CYP2C19 polymorphism for optimised dosage regimens in patients with invasive fungal infections.
Int J Antimicrob Agents 2014;44:436-42.
PubMed PMID: 25239277.</td><td>3

*1/*17:
AA
IM: AA
PM: A</td><td>144 patients were treated with intravenous and/or oral voriconazole for a median of 35 days (16-81 days). The dose was determined based on the SmPC. Trough concentrations were determined a median of 8 days (3-51 days) after the first dose. There was no significant difference in trough concentration between oral and intravenous administration. Co-medication with other antimycotics was excluded, but other relevant co-medication was not.
A successful response was defined as a reduction or disappearance of clinically relevant symptoms of fungal infection (fever and infection markers), reduction or disappearance of signs on a computer tomography scan (CT) or magnetic resonance image scan (MRI) or proven or assumed eradication of the fungus (negative culture results). A lack of response was defined as the absence of a response after 14 days or death as a result of the infection. Hepatotoxicity was defined as aspartate aminotransferase, alkaline phosphatase or alanine aminotransferase higher than 5 times the upper limit of normal, or total bilirubin more than 3 times the upper limit of normal (hepatotoxicity grade 3-4).

Genotyping:
- 3x *1/*17
- 62x *1/*1
- 62x IM
- 17x PM

Results:
<table>
<tr><td colspan="5">Results versus *1/*1:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>*1/*17</td><td>Value for *1/*1</td></tr>
<tr><td>trough concentration</td><td>x 1.9 (S)</td><td>x 1.2 (NS)</td><td>x 0.56 (NS)</td><td>1.98 µg/mL</td></tr>
<tr><td>hepatotoxicity</td><td colspan="3">NS (no difference between the groups)</td><td></td></tr>
<tr><td>efficacy</td><td colspan="3">NS (no difference between the groups)</td><td></td></tr>
<tr><td colspan="5">For *1/*17, the average trough concentration was higher than 1 µg/mL, but lower than 1.5 µg/mL (1.10 µg/mL).</td></tr>
<tr><td colspan="5">The results of this study were in agreement with a therapeutic range of 1.5-4 µg/mL (89.5% response, 12.3% hepatotoxicity). This was achieved in 39.6% of the patients in this study, in which the standard dose was used for all patients. 46.5% of the patients had a lower trough concentration and 13.9% had a higher trough concentration. Nevertheless, in the total group, efficacy occurred in 81.9% of the patients, hepatotoxicity in 12.5% and visual hallucinations in 1.4%.</td></tr>
<tr><td colspan="5">The authors indicate that the absence of a significant effect of the CYP2C19 genotype on hepatotoxicity and efficacy could be caused by the low number of PM and *1/*17.</td></tr>
</table></td><td>Authors’ conclusions: “Values of voriconazole C_{min} of poor metabolisers (PMs) were significantly higher than normal metabolisers and intermediate metabolisers. Model-based simulations showed that PM patients could be safely and effectively treated with 200 mg twice daily orally or intravenously, and non-PM patients with 300 mg twice daily orally or 200 mg twice daily intravenously. This study highlighted that voriconazole C_{min} is strongly influenced by CYP2C19 polymorphism, and gene-adjusted dosing is important to achieve therapeutic levels that maximise therapeutic response and minimise hepatotoxicity.”

Trough concentration$_{steady\ state}$ versus NM:
IM: 120%
PM: 190%</td></tr>
</table>

<table>
<tr><td>ref. 23, continuation</td><td></td><td>Note: The genotyped gene variants were not explicitly mentioned, but considering the definition of the genotype groups, *2, *3 and *17 must have been genotyped.</td><td></td></tr>
<tr><td>ref. 24
Liu P et al.
Population pharmacokinetic-pharmacodynamic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis.
Antimicrob Agents Chemother 2014;58:4727-36.
PubMed PMID: 24914120.</td><td>3

IM: AA
PM: AA</td><td>170 patients were treated with voriconazole for a planned duration of 6 weeks in combination with anidulafungin or placebo for the first 2-4 weeks. Voriconazole was administered as an intravenous loading dose of 6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily on days 2-7. The patient was then switched to oral voriconazole (300 mg 2x daily or 150 mg 2x daily for patients < 40 kg). Conversion to oral voriconazole was also possible at a later stage. Dose adjustment of voriconazole based on clinical response, side effects and/or voriconazole concentrations was permitted. Relevant co-medication was not excluded. Possible associations with outcome parameters were analysed with binary logistic regression.
A successful response was defined as a clinical improvement in combination with a radiographic improvement of more than 50%.
5 patients were not included in the effectiveness analyses, because they were treated for less than 3 days. The number of patients in the effectiveness analyses was 126, of which 55% on voriconazole monotherapy. The number of patients in the analyses for hepatic side effects was 170, of which 50% on voriconazole monotherapy. The number of patients in the analyses for psychiatric side effects was 142, of which 54% on voriconazole monotherapy.

Genotyping:
efficacy: - 84x NM - 35x IM - 7x PM
hepatic effect: - 115x NM - 48x IM - 7x PM
psychiatric effect: - 98x NM - 39x IM - 5x PM

Results:
<table><tr><td colspan="2">PM versus IM versus NM:</td></tr><tr><td>death during treatment</td><td>NS</td></tr><tr><td>response after 6 weeks</td><td>NS</td></tr><tr><td>hepatic side effects</td><td>NS</td></tr><tr><td>psychiatric side effects</td><td>NS</td></tr><tr><td colspan="2">In this study, no association was found between the exposure to voriconazole and clinical outcomes.</td></tr></table>
Note: The genotyped gene variants were not explicitly mentioned, but considering the definition of the genotype groups, at least *2 seem to have been genotyped. After *17, this is the most important gene variant in this American patient group.</td><td>Authors' conclusions: "Besides the drug exposures, no other covariates (i.e., CYP2C19 genotype status, age, weight, body mass index, sex, race, or neutropenia status) were identified as significant predictors of the efficacy and safety endpoints in invasive aspergillosis patients."</td></tr>
<tr><td>ref. 25
Zonios D et al.
Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype.
J Infect Dis 2014;209:1941-8.
PubMed PMID: 24403552.</td><td>3</td><td>92 patients aged 13-76 years were treated with voriconazole for 1-80 weeks. 54% of the patients received oral voriconazole at the start of the study. The dose varied from approx. 2.3 to approx. 9.3 mg/kg 2x daily. Trough concentrations were determined weekly from day 5 (steady state). If toxicity occurred on days 2-4, extra trough concentrations were determined. Doctors could request the voriconazole trough concentrations, but this hardly ever happened. Relevant co-medication was not excluded, but for the only patient in who a relevant effect of co-medication (phenytoin) on the voriconazole trough concentrations was observed, the samples from the period during which the co-</td><td>Authors' conclusions: "CYP2C19 and CYP2C9 genotypes had a minor influence over levels, though the 4 patients homozygous for the 2C19*2 genotype had higher average levels for voriconazole (4.3 vs 2.5 µg/mL)."</td></tr>
</table>

ref. 25, continuation

IM: AA
PM: A
*1/*9: AA
*1/*11: AA
*1/*15: AA
*1/*30: AA
*1/276C: A

*1/*17: AA
UM: AA

medication had an effect were not included.
The gene variant *17 could only be detected in 78 patients.
The listed values for the trough concentrations are averages of all determined values for the genotype group (1-17 per patient) and not averages of the values per patient.

Genotyping:

coding region:	*17:
- 63x *1/*1	- 45x *1/*1
- 19x IM	- 29x *1/*17
- 4x PM	- 4x UM
- 1x *1/*9	
- 1x *1/*11	
- 1x *1/*15	
- 1x *1/*30	
- 2x *1/276C	

Results:
Genotyping of coding region:

Parameters versus *1/*1:		
	trough concentration of voriconazole	hepatotoxicity
Value for *1/*1	2.468 µg/mL	6.3% in the entire group
IM	x 1.23 (NS)	no correlation with the genotype (NS)
PM	x 1.75 (S)	
*1/*9	x 0.75	
*1/*11	x 1.97	
*1/*15	x 0.06	
*1/*30	x 0.42	
*1/276C	x 1.64 (S)	
The dose of the patient with genotype *1/*15 was low (2.62 mg/kg 2x daily oral).		
The difference between *1/*1, *1/*2 and *2/*2 was somewhat bigger for the average value per patient than for the average value for all trough concentration determinations per genotype group.		
The recommended dose of 200 mg 2x daily did not always result in detectable voriconazole trough concentrations in adults. 9x *1/*1 and 1x *1/*15 had at least one non-detectable trough concentration of voriconazole on 200 mg 2x daily (2.6-4.7 mg/kg 2x daily).		
In this study, no association was found between the trough concentrations of voriconazole and metabolites and photosensitivity or hepatotoxicity. The occurrence of hallucinations was associated with higher voriconazole trough concentrations. This study also found no increase in the voriconazole trough concentrations over time. This auto-induction was expected, because voriconazole inhibits its own metabolism.		

Genotyping *17:

Trough concentration of voriconazole versus *1/*1 (2.89 µg/mL):	
*1/*17	x 0.79 (NS)
UM	x 1.26 (NS)
There was no effect of *17, not even when the presence or absence of *2 was taken into consideration.	

<table>
<tr><td>ref. 25, continuation</td><td></td><td>Note 1: Genotyping was performed for all gene variants (the coding and the promoter region were sequenced).

Note 2: As the activity of *9 is not well known and the activity of *11, *15, *30 (217C>T) and 276G>C is not known at all according to the allele nomenclature website (www.cypalleles.ki.se/cyp2c19.htm), the heterozygotes for these gene variants have not been added to IM, but instead have been listed separately.</td><td></td></tr>
<tr><td>ref. 26
Hicks JK et al. Voriconazole plasma concentrations in immunocompromised pediatric patients vary by CYP2C19 diplotypes. Pharmacogenomics 2014;15:1065-78. PubMed PMID: 25084200.</td><td>3

UM: A
*1/*17: AA
IM: A
PM: A</td><td>33 paediatric patients were treated with voriconazole. The initial recommended maintenance dose was 200 mg 2x daily for children aged 12 years and older (42% of the patients) and 7 mg/kg 2x daily for children younger than 12 years. The doses used varied from 3.6-16.1 mg/kg for children aged 12 years and older and from 2.6-41.2 mg/kg for children younger than 12 years. Trough concentrations were determined in steady state (minimum of 5 days after start of voriconazole without loading dose and minimum of 2 days after start with a loading dose or after conversion from intravenous to oral voriconazole). The number of determined trough concentrations per patient was 1-15 (median 3). A therapeutic range of 1-6 µg/mL was maintained.
Relevant co-medication was not excluded and not evenly distributed across the genotypes. A linear mixed-effects model found no significant effect of the different types of co-medication (other antimycotics (fluconazole or posaconazole), proton pump inhibitors and steroids), but the study possibly did not have sufficient power to demonstrate such a link.
A linear mixed-effects model was used to investigate the relationship between genotypes and the dose-corrected trough concentration. The listed values for the dose-corrected trough concentrations are median values of all determined values for the genotype group (1-15 per patient; median 3 per patient) and not median values of the values per patient.

Genotyping:
- 4x UM
- 8x *1/*17
- 11x *1/*1
- 9x IM
- 1x PM

Results:
<table>
<tr><td colspan="6">Parameters versus *1/*1:</td></tr>
<tr><td></td><td>UM</td><td>*1/*17</td><td>IM</td><td>PM</td><td>value for *1/*1</td></tr>
<tr><td>Median dose-corrected trough concentration (minimum and maxi-</td><td>x 0.14 (x 0.6 - x 0.034) (S)</td><td>x 0.71 (x 1 - x 0.86) (NS)</td><td>x 2.0 (x 1.3 - x 0.84) (S)</td><td>x 8.9 (x 157 - x 0.62) (S)</td><td>0.07 (0.003-1.47) µg.kg/mL.mg</td></tr>
<tr><td colspan="5">A linear mixed-effects model found a significant effect of the CYP2C19 genotype (S).</td></tr>
</table></td><td>Authors' conclusions: "Younger age and the presence of CYP-2C19 gain-of-function alleles were associated with subtherapeutic voriconazole concentrations. Starting doses based on age and CYP2C19 status could increase the number of patients achieving therapeutic voriconazole exposure."

Median dose-corrected trough concentration$_{steady\ state}$ versus NM:
UM: 17%
IM: 233%
PM: 1033%</td></tr>
</table>

<table>
<tr><td>ref. 26, continuation</td><td></td><td>
<table>
<tr><td>mum)</td><td colspan="4"></td><td></td></tr>
<tr><td rowspan="3">% of patients with a subtherapeutic average trough concentration (< 1 µg/mL)</td><td>x 3.7</td><td>x 1.4</td><td colspan="2">x 0</td><td>27%</td></tr>
<tr><td colspan="4">All UMs had a subtherapeutic trough concentration. The trough concentration did increase in these patients after a dose increase.</td></tr>
<tr><td colspan="4">Note: The dose in the Kinderformularium for patients < 12 years and for patients 12-15 years and < 50 kg (9 mg/kg 2x daily with a maximum of 350 mg 2x daily) is higher than the initially recommended maintenance dose. This affects more than 58% of the patients.</td></tr>
<tr><td>% of patients with a supratherapeutic average trough concentration (> 6 µg/mL)</td><td>x 0</td><td>x 1.4</td><td colspan="2">x 1.1</td><td>9.1%</td></tr>
<tr><td rowspan="4">Extrapolated 2x daily dose for a therapeutic concentration in most patients</td><td colspan="5">< 12 years</td></tr>
<tr><td>x 1.8</td><td>x 1.5</td><td>x 0.9</td><td>-</td><td>10 mg/kg</td></tr>
<tr><td colspan="5">≥ 12 years</td></tr>
<tr><td>x 2.0</td><td>x 1.0</td><td>x 0.71</td><td>x 0.29</td><td>7 mg/kg</td></tr>
</table>

Note: Genotyping was performed for 16 gene variants, of which only *2 (*2A and *2B) and *17 were found.</td><td></td></tr>
<tr><td>ref. 27
Kim SH et al. Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring of voriconazole in a Korean population. Infect Chemother 2013;45:406-14. PubMed PMID: 24475354.</td><td>3</td><td>104 patients were treated with voriconazole as a second-line antimycotic for at least 4 days (median of 166 days). The dose was initially based on the SmPC or on the following guideline: intravenous dose of 6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily or oral 200 mg 2x daily. The treatment was continued for at least 6 weeks or until the infection disappeared, unless breakthrough of invasive fungal infections or severe side effects occurred, or the patient died. The first trough concentration was determined at least 4 days (median of 6 days) after start of voriconazole. The number of determined trough concentrations per patient was an average of 4.9 and a median of 3. A therapeutic range of 1-5.5 µg/mL was maintained. Therapeutic drug monitoring was repeated on the fourth day after a change in the dose or route of administration, or in the case of suspected voriconazole toxicity or lack of response. For trough concentrations outside the therapeutic range, the dose was increased or reduced by 25-100%.</td><td>Authors' conclusions: "While none of the initial voriconazole trough levels in PMs was outside the target range, subtherapeutic initial trough levels were frequent in NMs. Although there was no significant relationship between CYP2C19 genotype and either the clinical outcomes of invasive aspergillosis or toxicity of voriconazole, further large-scale multicen-</td></tr>
</table>

<table>
<tr>
<td>ref. 27, continuation</td>
<td></td>
<td>Relevant co-medication was not excluded.
Efficacy and toxicity were determined 12 weeks after the start of voriconazole. A successful treatment was defined as a complete or partial response based on clinical, radiological and mycological data. Treatment failure was defined as no successful treatment, death or stop of voriconazole due to a breakthrough of invasive fungal infection or voriconazole-related side effects.
A breakthrough of an invasive fungal infection is defined as an infection that occurs more than 6 days after the start or less than 6 days after the end of voriconazole treatment.
Side effects were registered up to and including the third day after stopping treatment with voriconazole. Severe side effects were defined as side effects with grade 3-5 severity.

Genotyping:
- 39x NM
- 50x IM
- 15x PM

Results:
<table>
<tr><td colspan="4">Parameters versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>Median first trough concentration</td><td>x 1.8 (NS, trend, p = 0.062)</td><td>x 1.5 (S)</td><td>1.8 µg/mL</td></tr>
<tr><td>*1/*17: AA</td><td colspan="3">For the two *1/*17 in the NM group, the first trough concentration was 2.3 and 3.0 µg/mL and the median trough concentration was therefore 1.5x higher than in the entire NM group.</td></tr>
<tr><td rowspan="2">% of patients with a therapeutic first trough concentration (1-5.5 µg/mL)</td><td>x 1.9</td><td>x 1.4</td><td rowspan="2">54%</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM
All PM had a therapeutic first trough concentration.</td></tr>
<tr><td rowspan="2">% of patients with a subtherapeutic first trough concentration (< 1 µg/mL)</td><td>x 0</td><td>x 0.36</td><td rowspan="2">33%</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">% of patients with a supratherapeutic first trough concentration (> 5.5 µg/mL)</td><td>x 0</td><td>x 1.1</td><td rowspan="2">13%</td></tr>
<tr><td colspan="2">NS for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">Incidence of therapeutic trough concentrations (1-5.5 µg/mL)</td><td>x 2.6</td><td>x 1.5</td><td rowspan="2">23%</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
<tr><td rowspan="2">Incidence of subtherapeutic trough concentrations (< 1 µg/mL)</td><td>x 0.51</td><td>x 0.71</td><td rowspan="2">64%</td></tr>
<tr><td colspan="2">NS, trend for PM versus IM versus NM, p = 0.079</td></tr>
<tr><td rowspan="2">Incidence of supratherapeutic trough concentrations (> 5.5 µg/mL)</td><td>x 0.71</td><td>x 1.4</td><td rowspan="2">28%</td></tr>
<tr><td colspan="2">NS for PM versus IM versus NM</td></tr>
</table>
IM: AA#
PM: AA#</td>
<td>ter studies using clinical data from homogeneous populations are required.”

Median trough concentration$_{steady\ state}$ versus NM:
IM: 150%
PM: 180%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 27, continuation</td>
<td></td>
<td>
<table>
<tr><td>Failure of treatment</td><td>NS</td><td>NS</td><td>38%</td></tr>
<tr><td>Death (all causes)</td><td>NS</td><td>NS</td><td>28%</td></tr>
<tr><td>Death due to fungal infection</td><td>NS</td><td>NS</td><td>15%</td></tr>
<tr><td>All side effects</td><td>NS</td><td>NS</td><td>36%</td></tr>
<tr><td>Severe side effects</td><td>NS</td><td>NS</td><td>26%</td></tr>
<tr><td rowspan="2">Median treatment duration</td><td>x 1.5</td><td>x 1.8</td><td rowspan="2">82 days</td></tr>
<tr><td colspan="2">S for PM versus IM versus NM</td></tr>
</table>

Note 1: The initial dose recommended in this study corresponded to the initial dose for adults listed in the Informatorium Medicamentorum.

Note 2: Genotyping was performed for *2, *3 and *17.
</td>
<td></td>
</tr>
<tr>
<td>ref. 28
Racil Z et al.
Monitoring trough voriconazole plasma concentrations in haematological patients: real life multicentre experience.
Mycoses 2012;55:483-92.
PubMed PMID: 22429709.</td>
<td>3

IM: AA</td>
<td>124 patients were treated with voriconazole 100-600 mg 2x daily (median 200 mg 2x daily). This dose was equivalent to 1.1-13.65 mg/kg 2x daily (median 2.9 mg/kg 2x daily). In most cases, trough concentrations were determined because the doctor wanted to know the plasma concentration after the start of the treatment or following dose adjustment and sometimes due to suspected failure of treatment or a side effect. The doctor decided about any dose adjustments. Trough concentrations were determined 1-409 days (median 26 days) after start of voriconazole. The number of determined trough concentrations per patient was 1-27 (average of 4.7 and median of 3).
Relevant co-medication was not excluded.

Genotyping:
- 103x NM
- 39x IM

Results:
<table>
<tr><td colspan="2">Median voriconazole trough concentration versus NM (1.12 µg/mL):</td></tr>
<tr><td>IM</td><td>x 1.3 (NS, trend, p = 0.089)</td></tr>
</table>

Note 1: This study found no relationship between the voriconazole trough concentration and efficacy (n = 53) and between the voriconazole trough concentration and possible voriconazole toxicity. However, there were only 7 patients with possible voriconazole toxicity.

Note 2: Genotyping was performed for *2 and *3. In addition to *17, these are the most important gene variants in this Czech population group. *3 was not found in the 78 patients genotyped for *3.</td>
<td>Authors' conclusions: "With the exception of omeprazole administration, there was no relevant relationship between measured voriconazole concentrations and drug dose, route of administration, age, gender, CYP2C19*2 genotype, gastrointestinal tract abnormality, administration via naso-gastric tube, serum creatinine, and liver enzymes."</td>
</tr>
<tr>
<td>ref. 29
Driscoll TA et al.
Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised children and healthy adults.
Antimicrob Agents Chemother 2011;55:5770-9.</td>
<td>4</td>
<td>36 patients aged 2 to 12 years were treated prophylactically with voriconazole 7 mg/kg 2x daily intravenous for 7 days. AUC values were determined on day 7 (steady state).
Relevant co-medication was excluded, with the exception of corticosteroids.

Genotyping:
- 2x UM
- 11x *1/*1
- 22x (IM + *1/*17)
- 1x PM</td>
<td>Authors' conclusions: "Overall, voriconazole exposure in children could not be predicted based on CYP-2C19 genotype status in this study."</td>
</tr>
</table>

<table>
<tr>
<td>PubMed PMID: 21968355.

ref. 29, continuation</td>
<td>UM: AA</td>
<td>Results:
<table>
<tr><td colspan="3">Median $AUC_{0\text{-}12hours}$ versus *1/*1 (14.8 (5.02-64.7) µg.hour/mL):</td></tr>
<tr><td></td><td>UM</td><td>PM</td></tr>
<tr><td>Median $AUC_{0\text{-}12hours}$</td><td>x 2.5 (x 2.4 - x 0.93) (NS)</td><td>not determined</td></tr>
<tr><td></td><td colspan="2">The exposure to voriconazole could not be predicted based on the CYP-2C19 genotype (NS).</td></tr>
<tr><td colspan="3">A trough concentration higher than 1 µg/mL corresponded to an $AUC_{0\text{-}12hours}$ higher than 30 µg.hour/mL.</td></tr>
<tr><td colspan="3">The dose in the Kinderformularium for patients aged 2-12 years (9 mg/kg 2x daily on day 1, followed by 8 mg 2x daily) is higher than the dose used in this study.</td></tr>
</table>

Note: Genotyping was performed for *2-*5 and *17.</td>
<td>Median $AUC_{0\text{-}12hours}$ versus *1/*1:
UM: 250%</td>
</tr>
<tr>
<td>ref. 30
Driscoll TA et al. Comparison of pharmacokinetics and safety of voriconazole intravenous-to-oral switch in immunocompromised adolescents and healthy adults. Antimicrob Agents Chemother 2011;55:5780-9. PubMed PMID: 21911570.</td>
<td>4

UM: AA
PM: AA</td>
<td>18 patients aged 12 to 17 years were treated prophylactically with voriconazole. The dose was 6 mg/kg 2x daily intravenous on day 1, followed by 4 mg/kg 2x daily intravenous for 6 days and 300 mg 2x daily oral (or 150 mg 2x daily oral for one 12-year-old with genotype *1/*1 and weight < 40 kg (39.8 kg)) for 6.5 days. AUC values were determined on days 1 and 7 of the intravenous administration and on day 7 of oral treatment. Steady state was achieved on day 7.
Relevant co-medication was excluded, with the exception of corticosteroids.

Genotyping:
- 1x UM
- 6x *1/*1
- 9x (IM + *1/*17)
- 2x PM

Results:
<table>
<tr><td colspan="4">Median $AUC_{0\text{-}12hours}$ (lowest value – highest value) versus (*1/*1 + UM) (in µg.hour/mL):</td></tr>
<tr><td></td><td>UM</td><td>PM</td><td>value for (*1/*1 + UM)</td></tr>
<tr><td>Intravenous, day 1</td><td>x 1.2</td><td>x 1.7 (x 4.2 - x 0.59) (NS)</td><td>9.26 (2.52 - 19.8)</td></tr>
<tr><td>Intravenous, steady state</td><td>x 0.51</td><td>x 2.1 (x 5.0 - x 1.2) (NS)</td><td>16.3 (6.27 - 30.9)</td></tr>
<tr><td>Oral, steady state</td><td>x 1.0</td><td>x 2.7 (x 26 - x 1.3) (NS)</td><td>14.6 (1.17 - 37.9)</td></tr>
<tr><td>All time points</td><td colspan="3">The exposure to voriconazole could not be predicted based on the CYP2C19 genotype (NS).</td></tr>
<tr><td colspan="4">A trough concentration higher than 1 µg/mL corresponded to an $AUC_{0\text{-}12hours}$ higher than 20.7 µg.hour/mL.</td></tr>
<tr><td colspan="4">The intravenous and oral doses in the Kinderformularium for patients aged 12-15 years and < 50 kg (intravenous: 9 mg/kg 2x daily on day 1, followed by 8 mg/kg 2x daily; oral: 9 mg/kg 2x daily with a maximum of 350 mg 2x daily) is higher than the dose used in this study. The oral dose initially recommended in the Kinderformularium for patients aged 12-15 years and ≥ 50 kg and for patients ≥ 15 years (200 mg 2x daily, can potentially be increased to 300 mg 2x daily and for < 40 kg 100 mg 2x daily, can be increased to 150 mg 2x daily) is lower than the dose</td></tr>
</table>
</td>
<td>Authors' conclusions: "CYP2C19 status was not predictive of voriconazole exposure in immunocompromised adolescents in this study."

Median $AUC_{0\text{-}12hours,\ day\ 1}$ versus (*1/*1+ UM):
PM: 170%
UM: 120%

Median $AUC_{0\text{-}12hours,\ steady\ state}$ versus (*1/*1+ UM):
PM: 240%
UM: 75%</td>
</tr>
</table>

<table>
<tr><td>ref. 30, continuation</td><td></td><td>used in this study.

Note: Genotyping was performed for *2-*5 and *17.</td><td></td></tr>
<tr><td>ref. 31
Kim SH et al.
Voriconazole-related severe adverse events: clinical application of therapeutic drug monitoring in Korean patients.
Int J Infect Dis 2011;15:e753-8.
PubMed PMID: 21831685.</td><td>3

IM: AA
PM: AA</td><td>25 patients were treated with intravenous voriconazole for a median of 8 days. The dose was 6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily. Trough concentrations were determined a median of 6 days after start of voriconazole.
Relevant co-medication was not excluded.
Severe side effects were defined as side effects with grade 3-5 severity. A voriconazole-related severe side effect occurred in 32% of patients in the study (hepatotoxicity in 20% of patients, cardiotoxicity in 8% and neurotoxicity in 4%).
Univariate logistical regression was used to examine the effect of the CYP2C19 genotype on severe side effects.

Genotyping:
- 6x NM
- 17x IM
- 2x PM

Results:
<table>
<tr><td colspan="4">Parameters versus NM:</td></tr>
<tr><td></td><td>PM</td><td>IM</td><td>value for NM</td></tr>
<tr><td>Median first trough concentration</td><td>x 1.3
NS for PM versus IM versus NM</td><td>x 1.8</td><td>2.12 µg.hour/mL</td></tr>
<tr><td>% of patients with voriconazole-related severe side effects</td><td colspan="2">No significant difference for:
- IM+PM versus NM (NS)
- PM versus IM versus NM (NS)</td><td>12.5%</td></tr>
<tr><td colspan="4">The authors found a trough concentration ≥ 5.83 mg/L as the only independent risk factor for a voriconazole-related severe side effect.</td></tr>
</table>
Note: Genotyping was performed for *2 and *3. These are the most important gene variants in this Korean patient group.</td><td>Median trough concentration$_{steady\ state}$ versus NM:
IM: 180%
PM: 130%</td></tr>
<tr><td>ref. 32
Berge M et al.
Effect of cytochrome P450 2C19 genotype on voriconazole exposure in cystic fibrosis lung transplant patients.
Eur J Clin Pharmacol 2011;67:253-60.
PubMed PMID: 21038076.</td><td>3</td><td>24 patients aged 15-40 years were treated with voriconazole for at least 6 weeks. The initial dose according to the guidelines was (6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily intravenous or 200 mg 2x daily oral for patients > 40 kg). The voriconazole dose was then adjusted to achieve trough concentrations within the therapeutic range and to monitor interactions with immunosuppressants. A therapeutic range of 1-2 µg/mL was maintained. Trough concentrations outside the therapeutic range were defined as either > 3 µg/mL or < 0.5 µg/mL.
Relevant co-medication was not excluded.
The voriconazole maintenance dose was defined as the dose that resulted in a stable therapeutic concentration (at least three consecutive determinations within the therapeutic range of 1-2 µg/mL).

Genotyping:
- 1x UM</td><td>Authors' conclusions: "In this frail population of cystic fibrosis lung transplant recipients, voriconazole exposure is strongly influenced by CYP-2C19 genotype, and determining the genotype before voriconazole initiation may help determine the initial dosing regimen that will promptly achieve therapeutic plasma levels without producing out-of-range levels."</td></tr>
</table>

<table>
<tr>
<td>ref. 32, continuation</td>
<td>IM: A

(*1/*17+ UM): A</td>
<td>
- 7x *1/*17
- 6x *1/*1
- 10x IM

Results:
<table>
<tr><td colspan="5">Parameters versus *1/*1:</td></tr>
<tr><td></td><td>UM</td><td>*1/*17</td><td>IM</td><td>value for *1/*1</td></tr>
<tr><td rowspan="3">Maintenance dose (mg/kg)</td><td>approx x 1.3</td><td>approx x 1.0</td><td rowspan="2">x 0.70 (S)</td><td rowspan="3">6.8 mg/kg 2x daily</td></tr>
<tr><td colspan="2">NS for (*1/*17 + UM)</td></tr>
<tr><td colspan="3">S for (*1/*17 + UM) versus *1/*1 versus IM</td></tr>
<tr><td rowspan="3">Maintenance dose (mg)</td><td>approx x 1.3</td><td>approx x 0.90</td><td>x 0.70</td><td rowspan="3">317 mg 2x daily</td></tr>
<tr><td colspan="3">S for (*1/*17 + UM) versus *1/*1 versus IM</td></tr>
<tr><td colspan="5">Multivariate logistical regression revealed that CYP2C19 gene variants are responsible for 38% of the variation in the maintenance dose.</td></tr>
<tr><td colspan="5">Note: The average maintenance dose found for *1/*1 is 1.6-1.7 and 1.7-3.2 times higher than the doses listed in the Informatorium Medicamentorum and Kinderformularium for patients aged 15 years and older and ≥ 40 kg (75% of the patients in this study) (200 mg 2x per day oral or 4 mg/kg intravenous) and < 40 kg (25% of the patients in this study) (100 mg 2x per day oral or 4 mg/kg intravenous) respectively.
The authors have indicated that this is possibly due to the fact that these are patients with cystic fibrosis. Cystic fibrosis reduces the absorption of many medicines.</td></tr>
<tr><td rowspan="2">Time to maintenance dose</td><td colspan="2">x 1.9</td><td>x 2.9</td><td rowspan="2">36 days</td></tr>
<tr><td colspan="3">NS, trend for the difference between (*1/*17 + UM), *1/*1 and IM, p = 0.11</td></tr>
<tr><td rowspan="2">Median time to the first trough concentration in the therapeutic range (1-2 µg/mL)</td><td colspan="2">x 2.4</td><td>x 2.9</td><td rowspan="2">4 days</td></tr>
<tr><td colspan="3">S for the difference between (*1/*17 + UM), *1/*1 and IM</td></tr>
<tr><td rowspan="2">% of subtherapeutic trough concentrations (< 0.5 µg/mL) per patient in the first 42 days</td><td colspan="2">x 2.4</td><td>x 0.83</td><td rowspan="2">15.6%</td></tr>
<tr><td colspan="3">S for (*1/*17 + UM) versus *1/*1 and IM</td></tr>
<tr><td rowspan="2">% of supratherapeutic trough concentrations (> 3 µg/mL) per patient in the first 42 days</td><td colspan="2">x 0.56</td><td>x 2.6</td><td rowspan="2">12.1%</td></tr>
<tr><td colspan="3">S for IM versus *1/*1 and (*1/*17 + UM)</td></tr>
<tr><td>% of patients with side effects</td><td colspan="3">NS for the difference between (*1/*17 + UM), *1/*1 and IM</td><td>83.3%</td></tr>
</table>
Note: Genotyping was performed for *2 and *17. These are the most important gene variants in this Caucasian patient group.
</td>
<td>Maintenance dose versus *1/*1:
UM: 130%
IM: 70%</td>
</tr>
</table>

<table>
<tr>
<td>ref. 33
Brüggemann RJ et al.
Pharmacokinetics and safety of 14 days intravenous voriconazole in allogeneic haematopoietic stem cell transplant recipients.
J Antimicrob Chemother 2010;65:107-13.
PubMed PMID: 19933691.</td>
<td>3

IM: AA</td>
<td>10 patients weighing more than 63 kg were treated with intravenous voriconazole for 2 weeks (6 mg/kg 2x daily on day 1, followed by 4 mg/kg 2x daily).
Relevant co-medication was not excluded, but there was no evidence for interactions between voriconazole and the medicines given as co-medication. All patients received cyclosporin 2 mg/kg 2x daily intravenous from day 7.
One patient with an unknown genotype was not included in the study, because voriconazole was stopped prematurely due to a possible voriconazole-related skin rash.

Genotyping:
- 4x NM
- 6x IM

Results:
<table>
<tr><td colspan="4">Parameters versus NM:</td></tr>
<tr><td colspan="2"></td><td>IM</td><td>value for NM</td></tr>
<tr><td colspan="2">Median clearance on day 7</td><td>x 0.55 (NS)</td><td>15.52 L/hour</td></tr>
<tr><td colspan="2">Median clearance on day 14</td><td>x 0.69 (NS)</td><td>14.15 L/hour</td></tr>
<tr><td rowspan="2">Trough concentration on day 7</td><td>average</td><td>x 1.4 (NS)</td><td>1.18 µg/mL</td></tr>
<tr><td>median</td><td>x 1.8 (NS)</td><td>0.88 µg/mL</td></tr>
<tr><td rowspan="2">$AUC_{0\text{-}12hours}$ on day 7</td><td>average</td><td>x 1.3 (NS)</td><td>27.0 µg.hour/mL</td></tr>
<tr><td>median</td><td>x 1.7 (NS)</td><td>22.7 µg.hour/mL</td></tr>
<tr><td rowspan="2">Trough concentration on day 14</td><td>average</td><td>x 0.69 (NS)</td><td>2.22 µg/mL</td></tr>
<tr><td>median</td><td>x 2.0 (NS)</td><td>0.74 µg/mL</td></tr>
<tr><td rowspan="2">$AUC_{0\text{-}12hours}$ on day 14</td><td>average</td><td>x 0.74 (NS)</td><td>40.6 µg.hour/mL</td></tr>
<tr><td>median</td><td>x 1.2 (NS)</td><td>24.3 µg.hour/mL</td></tr>
<tr><td colspan="4">For NM, 50% and 75% of the trough concentrations on day 7 and day 14 respectively were lower than 1 µg/mL; for IM this was 17% in both cases (significance not determined).</td></tr>
<tr><td colspan="4">As the differences between average and median values and between day 7 and day 14 demonstrate, there were large interindividual and intra-individual variations in the kinetic parameters.</td></tr>
<tr><td colspan="2">% of patients with visual side effects</td><td>NS</td><td>75%</td></tr>
<tr><td colspan="2">Other side effects</td><td>NS</td><td></td></tr>
</table>
Note: Genotyping was performed for *2 and *3. After *17, these are the most important gene variants in this Dutch patient group.</td>
<td>Authors' conclusions: "No difference in clearance of voriconazole was found between CYP2C19 normal metabolizers (n=4) and carriers of one non-functional allele (n=6)."

Trough concentration$_{steady\ state}$ versus NM:
IM: 140%

Median trough concentration$_{steady\ state}$ versus NM:
IM: 180%</td>
</tr>
<tr>
<td>ref. 34
Matsumoto K et al.
Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes.</td>
<td>3

IM+PM: AA</td>
<td>29 patients, 10x NM, 19x IM+PM, voriconazole 6 mg/kg 2x daily for 1 day, followed by 3.6 ± 0.8 mg/kg 2x daily for 3-470 days, no relevant co-medication.

IM+PM versus NM:
- There was no significant relationship between hepatotoxicity and CYP2C19 phenotype.
- Decrease in the maintenance dose by 14% (NS, from 7.8 to 6.7 mg/kg per day).</td>
<td>Authors' conclusion: "Non-linear pharmacokinetic analysis suggested that voriconazole therapy should be initiated with a dose of 7.2–8.9 mg/kg/day for CYP2C19 wild-type</td>
</tr>
</table>

Int J Antimicrob Agents 2009;34:91-4. **ref. 34, continuation**		- Decrease in the maintenance dose in the patients with hepatotoxicity by 17% (NS, from 8.3 to 6.9 mg/kg per day). - Non-linear pharmacokinetic model: decrease in the dose that corresponds to a trough concentration of 2-4 mg/L by 27-39% (NS, from 7.2-8.9 to 4.4-6.5 mg/kg per day). Goodwin et al., 2008 found an increased incidence of hepatotoxicity at trough concentrations > 4 mg/L (increase from 5.9% to 75%). Note: Significances unknown.	and 4.4–6.5 mg/kg/ day for the non-wild-type in Japanese patients.'
ref. 35 Lei HP et al. Lack of effect of Ginkgo biloba on voriconazole pharmacokinetics in Chinese volunteers identified as CYP-2C19 poor and extensive metabolizers. Ann Pharmacother 2009;43:726-31.	3 PM: A	14 healthy volunteers, 7x NM, 7x PM (*2/*2), received a single dose of 200 mg voriconazole, no co-medication, coffee or alcohol, no smokers; PM versus NM: - Increase in median AUC by 305% (S; from 5.17 to 20.96 mg.h/L). - Decrease in median Cl_{or} by 75% (S; from 644.85 to 159.01 mL/min). - Increase in median $t_{1/2}$ by 244% (S; from 3.27 to 11.26 h). No severe side effects.	Authors' conclusion: "CYP2C19 genotype is a major determinant influencing voriconazole metabolism." (median AUC versus NM, single dose: PM: 405%)
ref. 36 Wang G et al. The CYP2C19 ultrarapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 2009;65:281-5.	3 PM: A *17: A	20 healthy volunteers, 12x NM (8x *1/*1, 4x *1/*17), 8x PM (*2/*2), received a single dose of 200 mg voriconazole, no co-medication and no coffee or alcohol for 7 days before the study, no smokers; PM versus *1/*1: - Increase in AUC by 245% (S; from 6.92 to 23.9 mg.h/L). - Decrease in Cl_{or} by 72% (S; from 521.53 to 146.7 mL/min). - Increase in $t_{1/2}$ by 69% (S; from 8.28 to 13.98 h). *1/*17 versus *1/*1: - Decrease in AUC by 48% (S; from 6.92 to 3.63 mg.h/L). - Increase in Cl_{or} by 79% (S; from 521.53 to 932.02 mL/min). - Decrease in $t_{1/2}$ by 13% (NS; from 8.28 to 7.19 mg.h/L) Significant effect of the *17 allele on the pharmacokinetics.	Authors' conclusion: "Our data indicate that the presence of the CYP2C19*17 allele results in ultrarapid metabolism of voriconazole after a single oral dose." (AUC versus *1/*1, single dose: PM: 345%)
ref. 37 Karlsson MO et al. Population pharmacokinetic analysis of voriconazole plasma concentration data from pediatric studies. Antimicrob Agents Chemother 2009;53:935-44.	4	Population pharmacokinetic analysis of data obtained from 3 studies. 82 children, 58x NM, 24x IM+PM (21x IM, 3x PM), single dose of voriconazole 3 or 4 mg/kg intravenous (n=11) or 2x daily intravenous voriconazole 6 mg/kg on day 1, followed by 3 mg/kg on days 2-4 and 4 mg/kg on days 4-8 (n=28) or 2x daily intravenous voriconazole 6 mg/kg on day 1, 4 mg/kg on days 2-4, 6 mg/kg on days 5-8, followed by 2x daily oral voriconazole 4 mg/kg on days 9-12 or 2x daily intravenous voriconazole 6 mg/kg on days 1-4, 8 mg/kg on days 5-8, followed by 2x daily oral voriconazole 6 mg/kg on days 9-12 (n=43), co-medication not excluded. No raw data, only results from the pharmacokinetic model: - The CYP2C19 phenotype is a statistically significant	Authors' conclusion: "Loading doses or individual dosage adjustments according to baseline covariates (a.o. CYP-2C19 fenotype) are not considered necessary in administering voriconazole to children."

ref. 37, continuation	IM+PM: A	co-variable for the prediction of the plasma concentration (S). - The model predicts a decrease in the clearance by 35.5% for IM+PM. - The model predicts that a dose adjustment to 7 mg/kg 2x daily or 200 mg 2x daily based on the CYP2C19 phenotype will not result in an improved concurrence with the exposure found for a dose of 4 mg/kg 2x daily in adults. Co-medication with CYP450 inducers or CYP2C19 inhibitors was not a statistically significant co-variable.	
ref. 38 Weiss J et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol 2009;49:196-204.	3 PM: A IM: A *17: A	Analysis of the combined data from Mikus et al., 2006 and Rengelshausen et al., 2005 after additional determination of *17 alleles. 35 healthy volunteers, 10x NM+IM (8x *1/*17, 2x *2/*17), 9x NM (*1/*1), 11x IM (*1/*2), 5x PM (5x *2/*2), received a single dose of 400 mg voriconazole, no co-medication; Multiple regression analysis: - The number of functional genes has a significant effect on AUC, Cl_{or} and $t_{1/2}$ and predicts up to 50% of the parameter variability (39% of the variability in AUC) (S). PM versus *1/*1: - Increase in AUC by 178% (S; from 16.44 to 45.73 mg.h/L). - Decrease in Cl_{or} by 65% (S; from 465.5 to 162.9 mL/min). - Increase in $t_{1/2}$ by 98% (S; from 7.23 to 14.28 h). *1/*2 versus *1/*1: - Increase in AUC by 56% (S for the trend NM+IM, NM, IM and PM; from 16.44 to 25.66 mg.h/L). - Decrease in Cl_{or} by 31% (S for the trend; from 465.5 to 319.2 mL/min). - Increase in $t_{1/2}$ by 14% (S for the trend; from 7.23 to 8.25 h). (*1/*17 + *2/*17) versus *1/*1: - Decrease in AUC by 19% (S for the trend NM+IM, NM, IM and PM; from 16.44 to 13.27 mg.h/L). - Increase in Cl_{or} by 13% (S for the trend; from 465.5 to 526.9 mL/min). - Decrease in $t_{1/2}$ by 3.7% (S for the trend; from 7.23 to 6.96 h). - The abovementioned data point to a significant effect of the *17 allele on the pharmacokinetics.	Authors' conclusion: "The number of variant CYP2C19 alleles explains a substantial part of the wide variability of voriconazole pharmacokinetics." (AUC versus NM (*1/*1 + *1/*17), single dose: PM: 305% IM (*1/*2 + *2/*17): 158%)
ref. 39 Levin MD et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. J Antimicrob Chemother 2007;60:1104-7.	3 IM+PM: AA	86 immune-compromised patients, 63x NM, 23x IM+PM, 2x daily oral voriconazole 6 mg/kg on 1 day, 4 mg/kg on days 2-7, 200 mg thereafter (n=74) or intravenous voriconazole during days 1-7 followed by oral administration (n=12); relevant co-medication not excluded. IM+PM versus NM: - No significant increase in the maximum concentration of bilirubin, ALP, GGT, ASAT or ALAT (NS). - No significant increase in the elevation of the concentration of bilirubin, ALP, GGT, ASAT or ALAT (NS).	Authors' conclusion: "No significant relationship between CYP2C9, CYP2C19 or CYP3A5 polymorphisms and serum liver enzyme levels was observed in patients treated with voriconazole."

ref. 39, continuation		- No significant increase in the maximum degree of toxicity according to the common toxicity criteria (CTC; distinguishes between 5 degrees of toxicity) for bilirubin, ALP, GGT, ASAT or ALAT (NS). - No significant increase in the percentage of patients with an increase of ≥ 2 degrees of toxicity according to the CTC for bilirubin, ALP, GGT, ASAT or ALAT (NS). - No significant increase in the percentage of patients with a maximum toxicity grade ≥ 2 according to the CTC for bilirubin, ALP, GGT, ASAT or ALAT (NS).	
ref. 40 Mikus G et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. Clin Pharmacol Ther 2006;80:126-35.	3 PM: A IM: A	20 healthy volunteers, 4x *2/*2+*2/*3+*3/*3, 8x *1/*2+*1/*3, 8x *1/*1, received a single dose of 400 mg voriconazole, no co-medication; - PM (*2/*2+*2/*3+*3/*3): increase in the AUC voriconazole versus NM from 16.52 to 47.96 h·µg/mL (S by 190%), decrease in Cl_{or}[a] from 6.34 to 2.21 mL/min/kg (S by 65%), increase in t½ from 8.11 to 15.21 hours (S by 88%). - IM (*1/*2+*1/*3): increase in the AUC voriconazole versus NM from 16.52 to 22.65 h·µg/mL (NS by 37%), decrease in Cl_{or}[a] from 6.34 to 4.69 mL/min/kg (S by 26%), decrease in t½ from 8.11 to 8.07 hours (NS by 0.4%). No severe side effects.	(AUC versus NM, single dose: PM: 290% IM: 137%)
ref. 41 Rengelshausen J et al. Opposite effects of short-term and long-term St John's wort intake on voriconazole pharmacokinetics. Clin Pharmacol Ther 2005;78:25-33.	3 PM: AA IM: AA	16 healthy volunteers, 2x *2/*2, 6x *1/*2, 9x *1/*1, received a single dose of 400 mg voriconazole, no co-medication; - *2/*2: increase in the AUC of voriconazole versus *1/*1 from 14.3 to 37.1 h·µg/mL (by 159%). - *1/*2: increase in the AUC of voriconazole versus *1/*1 from 14.3 to 31.2 h·µg/mL (by 118%). - *1/*2+*2/*2: increase in AUC of voriconazole from 14.3 to 32.7 h·µg/mL (S by 129%), decrease in Cl_{or} versus *1/*1 from 493 to 287 mL/min (S by 42%). No severe side effects. Note: significances of separate phenotypes unknown.	(AUC versus NM, single dose: PM: 259% IM: 218%
ref. 42 Ikeda Y et al. Pharmacokinetics of voriconazole and cytochrome P450 2C19 genetic status. Clin Pharmacol Ther 2004;75:587-8.	2 PM: AA IM: AA	12 healthy volunteers, 2x PM, 4x IM, 6x NM, 6 individuals receiving 400 mg/day voriconazole for 10 days, 6 individuals receiving 600 mg/day voriconazole for 10 days, no co-medication; - PM: at 400 mg/day, the AUC is 5.8x higher than for NM, at 600 mg/day it is 3.8x higher. C_{max} is approximately 3x higher. 1 PM with dose 600 mg/day had elevated liver function test results. - IM: at 400 mg/day, the C_{max} was unchanged for 1 IM versus NM and the C_{max} was increased for 1 IM (no percentage available). Note: genotype unknown, significances unknown.	(AUC versus NM: PM: 580%)
ref. 43 SmPC VFEND (voriconazole) 20-04-21 a.o.[b]	0	<u>Pharmacokinetics</u> In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5%. Studies conducted in Caucasian and	

ref. 43, continuation	PM: A IM: A	Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_T) than their homozygous normal metaboliser counterparts. Subjects who are heterozygous normal metabolisers have on average 2-fold higher voriconazole exposure than their homozygous normal metaboliser counterparts.	AUC versus NM: PM: 400% IM: 200%

[a] corrected for body weight
[b] SmPC VFEND (voriconazole) 13-10-21, USA, contains the same information.

Risk group	IM with CYP2C19 inhibitors, IM and PM with CYP3A inhibitors or substrates, UM with CYP2C19 and/or CYP3A inducers

Comments:

- Genotype-guided dosing studies were only included if at least two of the phenotype groups studied consisted of at least 5 patients. For the period after 2009, studies including healthy volunteers were not included. Studies suggest an effect of the disease on the plasma concentration of voriconazole (Encalada Ventura MA et al. Longitudinal analysis of the effect of inflammation on voriconazole trough concentrations. Antimicrob Agents Chemother 2016;60:2727-31. PubMed PMID: 26883707 and Chawla PK et al. Correlation of CYP2C19 genotype with plasma voriconazole levels: a preliminary retrospective study in Indians. Int J Clin Pharm 2015;37:925-30. PubMed PMID: 26024717). Furthermore, the dose of voriconazole in patients is often set based on therapeutic drug monitoring, whilst this is not the case in healthy volunteers. For these reasons, studies involving healthy volunteers provide only limited information about the importance of the gene-drug interaction in the treatment of patients.
  Case descriptions were not included for the period after 2009, as they do not contribute sufficiently to the burden of proof.
  For the period after 2009, articles with pharmacokinetic or pharmacokinetic-pharmacodynamic models were only included if they also contained new data, in other words if they were not based solely on previously published data. In addition, kinetic studies – in contrast to meta-analyses – were only included if data was presented per genotype group and the percentage of the kinetic parameters versus NM or *1/*1 could be calculated. If IM was the only variant genotype group in the kinetic study, the study was only included if the number of IM was greater than 3. Other studies did not provide enough additional information.
  Studies in liver transplant patients were not included, because the genotype of the liver of these patients may differ from that of the rest of the body.
  Miao 2019 (Miao Q et al. Correlation of CYP2C19 genotype with plasma voriconazole exposure in South-western Chinese Han patients with invasive fungal infections. Medicine (Baltimore) 2019;98:e14137. PMID: 30653146) was not included in the risk analysis, because the dose-corrected trough concentration was expressed in µg/ml per kg/day instead of µg/ml per mg/kg, and in addition, was higher than the not dose-corrected trough concentration, while the dose was higher than 1 mg/kg. For this reason, it is not clear how the dose-corrected trough concentration was calculated and whether data are reliable.
  Ebrahimpour 2017 (Ebrahimpour S et al. Impact of CYP2C19 polymorphisms on serum concentration of voriconazole in Iranian hematological patients. J Res Pharm Pract 2017;6:151-7. PMID: 29026840) was not included in the risk analysis, because the mean voriconazole serum concentration values reported for *1/*1 and *1/*17 in the text differ from the ones depicted in the figure. As a result, reliable concentration data were lacking.
- The effect of co-medication on the exposure to voriconazole can differ for the different CYP2C19 genotypes. Co-medication that results in the induction of CYP2C19 and inhibition of CYP3A (ritonavir + atazanavir) reduces the exposure to voriconazole in NM and increases the exposure in PM (Zhu L et al. CYP2C19 genotype-dependent pharmacokinetic drug interaction between voriconazole and ritonavir-boosted atazanavir in healthy subjects. J Clin Pharmacol 2016 Jul 19 [Epub ahead of print]. PubMed PMID: 27432796).
  The CYP3A4 substrate tacrolimus enhances the exposure to voriconazole in PM, but not significantly in NM (Mochizuki E et al. A case of treatment with voriconazole for chronic progressive pulmonary aspergillosis in a patient receiving tacrolimus for dermatomyositis-associated interstitial lung disease. Respir Med Case Rep 2015;16:163-5. PubMed PMID: 26744690).
- Algorithm:
- Teusink A et al. Genotype-directed dosing leads to optimized voriconazole levels in pediatric patients receiving hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2016;22:482-6. PubMed PMID: 26616742.
  In the case of genotype-guided prophylaxis, the dose started at 7 mg/kg 2x daily for paediatric patients with genotype NM or UM, at 6 mg/kg 2x daily for IM and patients with unknown genotype and 5 mg/kg 2x daily for PM. Voriconazole trough concentrations were always determined after 8 doses (both after start of treatment and after dose changes). The dose was adjusted until the trough concentration was within the therapeutic range (1-5.5 µg/mL). If the trough concentration was lower than the detection limit (0.1 µg/mL), the dose was increased by 50%

and if the trough concentration was 0.1-1 µg/mL, the dose was increased by 25%. If the trough concentration was higher than 5.5 µg/mL, then two doses were skipped and this was followed by 50-75% of the previous dose. After achieving the therapeutic range, the trough concentration was checked every week for 1 month and then every 2 weeks until end of treatment. Extra trough concentration determinations were performed if there were indications of voriconazole toxicity or a fungal infection.
This dose algorithm reduced the time to reach the therapeutic range compared to an algorithm in which all patients were started on 5 mg/kg 2x daily and the voriconazole trough concentration was also determined after 8 doses in each case.
Note: The children in this study were mostly younger than 12 years of age. In this case, the Kinderformularium recommends an intravenous initial dose of 9 mg/kg 2x daily, followed by an intravenous dose of 8 mg/kg 2x daily and finally an oral dose of 9 mg/kg 2x daily. De hoofdvraag waarvoor we een risicoanalyse maken, is de vraag of bij een patiënt waarvan bekend is dat deze het genotype heeft dat problemen geeft (in dit geval dus HLA-B*5701) de behandeling moet worden aangepast. Of er moet worden gegenotypeerd is een tweede vraag. Op basis van de Clinical Implications Score geldt voor flucloxacilline: The KNMP Pharmacogenetics Working Group considers genotyping before starting flucloxacillin to be beneficial for drug

- safety. It is advised to consider genotyping these patients before (or directly after) drug therapy has been initiated to
- guide drug selection. Dit betekent dat als dit voorstel wordt gevolgd, er geen sterke aanbeveling is om te genotyperen. Het kan worden overwogen. De reden is dat het risico op DILI ook in patiënten met HLA-B*5701 klein blijft.
- De DILI-casus In Nicoletti 2019 gebruikten flucloxacilline overigens gedurende gemiddeld 10 dagen, dus werd flucloxacilline gemiddeld op dag 11 van de kuur gestaakt. Voor personen met een eerste kuur is dit dus minder dan 3 weken.
- <u>Other guidelines</u>:
  - Moriyama B et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther 2017;102:45-51. PubMed PMID: 27981572.
    The authors based their guideline on 36 articles. As the selection of their articles took place in May 2016, the study by Wang 2016, which found higher voriconazole trough concentrations for PM, and the meta-analysis by Li 2016, which found an increased efficacy for PM, do not form part of this guideline. However, these articles were included in our risk analysis. Most of the articles included by CPIC were also included in our risk analysis (60% of the 10 articles involving healthy volunteers and 50% of the 26 articles involving patients). 10 of the 13 articles involving patients, which were not included in our risk analysis, involved case reports.
    Although voriconazole is used for prophylaxis of invasive aspergillosis in high-risk patients with neutropenia or haematopoietic stem cell transplantation, the focus of the recommendations in the CPIC guideline rests on the treatment of invasive fungal infections using voriconazole.
    PM:
    The authors indicate that there is substantial evidence for a link between the CYP2C19 genotype and the pharmacokinetics of voriconazole and that the evidence is of high quality in most cases. However, in the table that they refer to, a high degree of evidence for reduced voriconazole metabolism is found only for healthy PM. For patients and for other genotypes, the degree of evidence is moderate or even weak. The authors indicate that the evidence for an association between PM and side effects is limited to a single case (Moriyama B et al. Pharmacokinetics of intravenous voriconazole in obese patients: implications of CYP2C19 homozygous poor metabolizer genotype. Pharmacotherapy 2013;33:e19-22). However, according to the authors, a strong association was found between PM and increased voriconazole concentrations. As increased voriconazole concentrations result in side effects, the use of an alternative for voriconazole is recommended for PM. The authors indicate that there are also cases in which voriconazole was stopped in PM due to increased and potentially toxic concentrations. In addition to the previously mentioned case of Moriyama 2013, the table mentions a second case (Moriyama B et al. Prolonged half-life of voriconazole in a CYP2C19 homozygous poor metabolizer receiving vincristine chemotherapy: avoiding a serious adverse drug interaction. Mycoses 2011;54: e877-9). The table also mentions that four studies (Levin 2007, Matsumoto 2009, Bergé 2011 and Kim 2013) found no association between the CYP2C19 genotype and side effects. Although clinical studies did not consistently show an association between the CYP2C19 genotype and side effects, CPIC recommends the use of a different antimycotic for PM. The reason is that individual PMs can have elevated plasma concentrations, which can result in toxicity. If voriconazole is strongly indicated for the treatment of an invasive fungal infection in a PM, then administration of a lower dose with thorough therapeutic drug monitoring is an option. CPIC classifies the advice for PM as moderate.
    *UM and *1/*17:*
    The authors indicate that the therapeutic recommendation for adult UMs is based on extrapolation of data for *1/*17, because these genotypes were not analysed separately in most studies. They also indicate that knowledge about UM and *1/*17 genotypes may help to prevent subtherapeutic plasma concentrations, which can result in failure of therapy. For UM and *1/*17, CPIC recommends using a different antimycotic, particularly because different cases demonstrate failure of voriconazole treatment in UM. The table lists three UMs, in which voriconazole was stopped due to non-detectable plasma concentrations or the absence of a response (Malingré

MM et al. A case report of voriconazole therapy failure in a homozygous ultrarapid CYP2C19*17/*17 patient co-medicated with carbamazepine. Br J Clin Pharmacol 2012;74:205-6; Abidi MZ et al. CYP2C19*17 genetic polymorphism--an uncommon cause of voriconazole treatment failure. Diagn Microbiol Infect Dis 2015;83:46-8 and Bennis Y et al. High metabolic N-oxidation of voriconazole in a patient with refractory aspergillosis and CYP-2C19*17/*17 genotype. Br J Clin Pharmacol 2015;80:782-4). The UM in Malingré 2012 used the CYP450 enzyme inducer carbamazepine as co-medication. The authors indicate that attempts to achieve therapeutic plasma concentrations in UM are often unsuccessful. Severe delays in achieving therapeutic concentrations in such patients with an active, invasive fungal infection can result in the progression of the disease. CPIC classifies the advice for UM and *1/*17 as moderate.

The authors indicate that there are various alternatives to voriconazole in the treatment of invasive fungal infections, including isavuconazole, formulations of amphotericin B with lipids and posaconazole. Isavuconazole is registered for the treatment of invasive aspergillosis and mucormycosis in adults. It is not registered for prophylaxis or for use in children. According to CPIC, there are currently only limited data about the use in children and isavuconazole is not listed in the Kinderformularium. Liposomal amphotericin B can be used instead of voriconazole for the treatment of invasive aspergillosis in adults and children. Amphotericin B is only registered for the prophylaxis of intestinal fungal infections, not for prophylaxis of invasive fungal infections. Posaconazole is registered for the treatment of invasive fungal infections in the case of intolerance for or inadequate effect of the standard treatment and for prophylaxis of invasive fungal infections in patients with a high risk of these. It can be used for both children and adults.

IM:

The authors indicate that it is not possible to give a medication recommendation for IM, due to the limited number of studies and the inconsistency of the results found. CPIC classifies the recommendation for IM as moderate.

The genotype-guided recommendations are:

UM, adults and children:		Select an alternative that is not metabolised by CYP2C19, such as isavuconazole, liposomal amphotericin B or posaconazole. Note: The recommendation for adults is based on extrapolated data for the genotype *1/*17.
*1/*17	adults:	Select an alternative that is not metabolised by CYP2C19, such as isavuconazole, liposomal amphotericin B or posaconazole.
	children:	Start with the standard dose and adjust the dose based on therapeutic drug monitoring. Note 1: Further dose adjustment or selection of an alternative could be possible due to other clinical factors, such as drug interactions, liver function, kidney function, race, site of infection, therapeutic drug monitoring and co-morbidities. Note 2: It is difficult to achieve therapeutic voriconazole concentrations in a timely manner in children with genotype UM or *1/*17. As critical time can be lost whilst trying to achieve therapeutic concentrations, an alternative is recommended, so that the child receives effective antimycotic treatment as soon as possible. Note 3: Thorough therapeutic drug monitoring is very important for patients with the *1/*17 genotype. As a result of the large variation in trough concentrations, there is insufficient proof to distinguish between paediatric patients with genotype *1/*17 and genotype *1/*1.
IM, adults and children:		Start with the standard dose. Note: Further dose adjustment or selection of an alternative could be possible due to other clinical factors, such as drug interactions, liver function, kidney function, race, site of infection, therapeutic drug monitoring and co-morbidities.
PM, adults and children:		Select an alternative that is not metabolised by CYP2C19, such as isavuconazole, liposomal amphotericin B or posaconazole. If voriconazole is considered the most suitable medicine, based on clinical recommendations, then voriconazole must be administered at a dose that is preferably lower than the standard dose and with thorough therapeutic drug monitoring. Note: The recommendation for children is based on extrapolated data from adults.

CPIC uses a different definition of NM (normal metaboliser) than the KNMP. *1/*17 is not categorised under NM, but is considered a separate phenotype (rapid metaboliser). CPIC indicates that statistical differences in average pharmacokinetic parameters between *1/*17 and *1/*1 have been observed, but that the range of the pharmacokinetic values found often overlaps (Li-Wan-Po A et al. Pharmacogenetics of CYP2C19: functional and clinical implications of a new variant CYP2C19*17. Br J Clin Pharmacol 2010;69:222-30 and Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther 2015;98:127-34). CPIC also indicates that it is not clear whether this definition of rapid metaboliser is suitable for all CYP2C19 substrates and therefore that the distinction could be specific to certain medicines. As the paediatric recommendation is the same for *1/*17 and NM, the different definition by the CPIC for NM for children is irrelevant. CPIC indicates that – for

children – there is insufficient proof to make a distinction between *1/*1 and *1/*17 due to the large variation in trough concentrations. However, for adults, CPIC does give a different recommendation for *1/*17 and *1/*1. CPIC indicates that – for adults – there is insufficient proof to make a distinction between *1/*17 and UM. The guideline does not provide a recommendation about whether patients should be genotyped or not. The authors indicate that a periodic update of the guideline is provided on the internet sites of the PharmGKB and CPIC. The abovementioned guideline was the most recent version as of 2 November 2021.

- Wang J et al. Model-oriented dose optimization of voriconazole in critically ill children. Antimicrob Agents Chemother 2021;65:e0049321. PMID: 34152812.
  Based on a population pharmacokinetic model, the maintenance dose for PM was calculated to be 60-70% that of NM for critically ill children aged 0.44-13.58 years,
  The population pharmacokinetic model was based on voriconazole plasma concentrations of 99 children with a median age of 5.25 years (range 0.44-13.58 years; mean 6.14 years), among whom 34 *1/*1, 45 IM, 14 PM and 1 *1/*17.
- Zubiaur P et al. Evaluation of voriconazole CYP2C19 phenotype-guided dose adjustments by physiologically based pharmacokinetic modeling. Clin Pharmacokinet 2021;60:261-70. PMID: 32939689.
  Based on a physiologically based pharmacokinetic model in healthy volunteers, the authors suggest that the standard dose may only be appropriate for NM, although they would benefit from a 50-100% loading dose increase. IM and PM required a daily dose reduction to 50% and 25% of the normal dose, respectively. *1/*17 and UM required a 2- and 4-fold higher dose, respectively.
  The physiologically based pharmacokinetic model was based on voriconazole plasma concentrations of 106 healthy volunteers receiving a single dose, including 4 UM, 33 *1/*17, 38 *1/*1, 29 IM and 2 PM, and steady state concentrations in 20 healthy volunteers receiving voriconazole for a period of 1 week. All data were from previously published studies. Physiologically based pharmacokinetic modelling was used to optimize voriconazole single-dose models for each CYP2C19 phenotype, which were extrapolated to steady state and evaluated for concordance with the therapeutic range of voriconazole.
- Liu Y et al. Model-based voriconazole dose optimization in Chinese adult patients with hematologic malignancies. Clin Ther 2019;41:1151-63. PMID: 31079860.
  Based on a population pharmacokinetic model, the recommended dose for IM and PM ≥ 60 years of age with diagnosed or suspected invasive fungal infection was calculated to be 50% and 25% of the mormal dose, respectively. Patients ≥ 60 years had a 2-fold higher exposure than patients aged 18-59 years.
  The population pharmacokinetic model was based on voriconazole plasma concentrations of 41 patients with hematologic malignancies and diagnosed or suspected invasive fungal infection, including 18 *1/*1, 16 IM, and 7 PM, and including 13 patients aged ≥ 60 years and 28 patients aged 18-59 years. Both efficacy and tolerability were considered in selecting the recommended doses.
- Kim Y et al. A personalized CYP2C19 phenotype-guided dosing regimen of voriconazole using a population pharmacokinetic analysis. J Clin Med 2019;8:227. PMID: 30744151.
  Based on a population pharmacokinetic model, the proposed initial dose for NM was twice the normal dose, for IM was the normal dose, and for PM was 50% of the normal dose,
  The population pharmacokinetic model was based on voriconazole plasma concentrations of 93 healthy volunteers and 100 patients from 5 previously published studies, of which 2 concerned single dosing and 1 concerned two single doses. The healthy volunteers included 32 NM, 27 IM and 34 PM. The patients included 43 NM, 43 IM and 14 PM. Only 1 of the NM was *1/*17.
- Lin XB et al. Population pharmacokinetics of voriconazole and CYP2C19 polymorphisms for optimizing dosing regimens in renal transplant recipients. Br J Clin Pharmacol 2018;84:1587-97. PMID: 29607533.
  Based on a population pharmacokinetic model in kidney transplant patients, the calculated required dose in the early postoperative period was 1.5 times the normal dose intravenously for NM, the normal dose intravenously or 1.75 times the normal dose orally for IM, and 75% of the normal dose intravenously or 1.25 times the normal dose orally for PM.
  The population pharmacokinetic model was based on voriconazole plasma concentrations of 105 patients, among whom 44 *1/*1, 49 IM, and 12 PM.

- <u>Cost-effectiveness</u>:
  - Patel JN et al. Evaluation of CYP2C19 genotype-guided voriconazole prophylaxis after allogeneic hematopoietic cell transplant. Clin Pharmacol Ther 2020;107:571-9. PMID: 31549386.
    In adult allogeneic hematopoietic cell transplant recipients, a CYP2C19 genotype-guided treatment was both cheaper and more effective than non-genotype-guided treatment (US$ 4,700 per patient lower costs and an invasive fungal infection rate of 0% instead of 6%). For the CYP2C19 genotype-guided treatment, *1/*1, IM and PM received the normal voriconazole dose and *1/*17 and UM received 1.5-fold the normal dose. Data for the CYP2C19 genotype-guided treatment were based on 89 patients: 3 UM, 29 *1/*17, 30 *1/*1, 23 IM, and 4 PM. The CYP2C19 genotype-guided treated patients were compared to simulated controls.
    The calculation was from the perspective of the health system. Direct medical costs were calculated for the first 100 days following hematopoietic cell transplantation. Direct medical costs consisted of drug and administration costs (different values for patients with voriconazole failure and voriconazole success), testing costs (including both genotyping and therapeutic drug monitoring costs), and invasive fungal infection costs, The cost of in-

house genotyping were approximately US$120 per patient. The cost of treating one invasive fungal infection is predicted to be roughly US$50,000 (O'Sullivan et al. Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among neutropenic patients in the United States. Value Health 2009;12:666-73). Data from the voriconazole arm of a randomized trial comparing voriconazole with itraconazole (Marks et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. Br J Haematol 2011;155:318-27) were used to create the cost estimates in the simulated control group. Costs described for the study cohort were applied to data from Marks 2011 on voriconazole dose (200 mg twice daily), success, failure, and alternative antifungals. In all analyses, if patients were switched to an alternative antifungal, the model assumed patients remained on the alternative drug for the duration of observation. Average per-patient cost for the study cohort were US$6,830 (US$5,760 for *1/*1+IM+PM and US$8,720 for *1/*17+UM). The per-patient cost for the simulated control arm was US$11,520, including a 6% rate of invasive fungal infections based on historical data (O'Sullivan 2019 and Girmenia et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). Biol Blood Marrow Transplant 2014;20:872-80) and more plasma level determinations due to higher rates of subtherapeutic concentrations with standard dosing.

While performing genotyping in-house costs approximately US$120 per patient, the cost of treating one invasive fungal infection is predicted to be roughly US$50,000 (O'Sullivan 2019). Therefore, even if 400 patients underwent genotyping to prevent one invasive fungal infection, the intervention would still be roughly cost neutral. Furthermore, using genotype-guided dosing allows for fewer plasma level determinations and lower costs associated with analysing concentrations compared with conventional dosing, given that more patients achieve target concentrations faster (though cost associated with plasma level determinations is nominal). Increased voriconazole success rates in our cohort compared with historical data also translated to less use of alternative (more expensive) antifungals.

The authors mention the following limitations of the cost-effectiveness study:

- Rates of invasive fungal infections are low in the post-allogeneic hematopoietic cell transplantation setting when patients receive antifungal prophylaxis, where historically 2-8% of patients experienced an invasive fungal infection (Marks 2011 and Girmenia 2014). Therefore, it is difficult to discern the true impact of genotype-guided dosing on clinical outcomes in this setting without performing a large randomized trial.
- The cost analysis was estimated based on simulated controls from prior published data, and the true cost is also unknown without conducting a randomized trial.
- Lastly, patients were only followed up to day + 100 post hematopoietic cell transplantation. There is a possibility that patients could have developed an invasive fungal infections after day + 100; however, data suggest that nearly 90% of invasive fungal infections are diagnosed within the first 100 days (Girmenia 2014).

- Mason NT et al. Budget impact analysis of CYP2C19-guided voriconazole prophylaxis in AML. J Antimicrob Chemother 2015;70:3124-6. PubMed PMID: 26233624.

In patients with acute myeloid leukaemia, a CYP2C19 genotype-guided treatment was both cheaper and more effective than non-genotype-guided treatment (US$ 415 per patient lower costs and 2.3 fewer patients annually with an invasive fungal infection per 100 treated patients). For the CYP2C19 genotype-guided treatment, *1/*1, IM and PM received the normal treatment with voriconazole and *1/*17 and UM received either a higher dose of voriconazole or an alternative. The most important cause of the cost-effectiveness was the fact that expensive antimycotic treatments and longer hospital stays were avoided (extra costs of US$ 30,952 per patient).

The calculation was based on a third party who paid for the treatment. The calculation used a model in which the medical costs were calculated for 1 year. The calculation was based on a price of US$ 44,752 for treatment of a non-infected patient during one cycle, a price of US$ 75,704 for treatment of a patient with a fungal infection during one cycle, a price of US$ 291.80 for a genetic test and a price of US$ 18.68 for determination of the plasma concentration of voriconazole. The treatment costs were average values. The price for a dose increase in or an alternative to voriconazole was therefore not included in the calculation. The incidence of fungal infection without prophylaxis (17.5%) and with voriconazole prophylaxis (6.6%) was obtained from the literature. The percentage of patients with a low voriconazole trough concentration as a result of a UM or *1/*17 genotype (56%) was obtained from an article including 10 paediatric patients with a voriconazole trough concentration ≤ 0.2 ug/mL, no CYP inducers and a known genotype for 9 of the patients (Hassan A et al. Modulators of very low voriconazole concentrations in routine therapeutic drug monitoring. Ther Drug Monit 2011;33:86-93. PubMed PMID: 21192313).

Even with variation of the input data (± 20%), the genotype-guided treatment remained both cheaper and more effective in all cases than the non-genotype-guided treatment. The incidence of fungal infection had the greatest effect. Genotype-guided prophylaxis would no longer be cost-saving at an incidence < 2%.

Date of literature search: 7 September 2021.

	Phenotype	Code	Gene-drug interaction	Action	Date
	PM	4 C	Yes	Yes	15 November 2021

KNMP Pharmacogenetics Working Group decision	IM	4 A	Yes	Yes	
	UM	4 A	Yes	Yes	

Mechanism:
Voriconazole is predominantly metabolised by CYP2C19 and to a lesser extent by CYP2C9 and CYP3A4. Voriconazole inhibits the activity of these three enzymes, resulting in non-linear kinetics for voriconazole. The most important metabolite, voriconazole-N-oxide, is inactive. Children metabolise voriconazole more rapidly than adults and the non-linear kinetics start at higher doses in children than in adults.
SmPC 12 March 2009: the pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. A disproportionate increase in exposure is observed at a higher dose. On average, it is estimated that an oral dose increase from 200 mg twice daily to 300 mg twice daily is equivalent to a 2.5-fold increase in exposure (AUC). Voriconazole has a narrow therapeutic range. A therapeutic range (based on trough concentrations) of 1-4 or 1-5.5 µg/mL is usually maintained. The risk of voriconazole-induced hepatotoxicity and other side effects increases with concentrations higher than 4 µg/mL. The NVZA mentions the following therapeutic ranges: pulmonal aspergillosis 1-6 µg/mL, badly penetrable areas such as cerebral infection, sinus infection 2-6 µg/mL. The NVZA indicates that it is recommended to lower the upper limit to 4 µg/mL in case of impaired liver function, In addition, the NVZA states that the role of therapeutic drug monitoring (TDM) of voriconazole only applies to Aspergillus species sensitive to voriconazole. There are no data on application of TDM in case of infections caused by yeast and other moulds, such as Scedosporium and Fusarium, or caused by less sensitive or resistant strains of Aspergillus fumigatus. Finally, the NVZA states that indications for target values for prophylaxis are lacking up to now. At the moment, for prophylaxis, the therapeutic limit of > 1 µg/mL is used.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	+
OR		
• Recommendation to genotype	++	
OR		
• At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++	
Total Score:	10+	1+
Corresponding Clinical Implication Score:		Potentially beneficial