Managing invasive aspergillosis: impact on health and personalized prevention or treatment strategies

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Chapter 5

Managing invasive aspergillosis in haematological patients in the era of resistance PCR and increasing triazole resistance: a modelling study of different strategies

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ABSTRACT

Objectives: Triazole resistance in *Aspergillus* spp. is emerging and complicates prophylaxis and treatment of invasive aspergillosis (IA) worldwide. New polymerase chain reaction (PCR) tests on bronchoalveolar lavage (BAL) fluid allow for detection of triazole-resistance on a genetic level, which opened up new possibilities for targeted therapy. In the absence of clinical trials, a modelling study delivers estimates of the added value of resistance detection with PCR and which empiric therapy would be optimal when local resistance rates are known.

Design: We performed a decision-analytic modelling study based on epidemiological data of IA, extended with estimated dynamics of resistance rates and treatment effectiveness. We compared six clinical strategies that differ in use of PCR diagnostics (used versus not used) and in empiric therapeutic choice in case of unknown triazole-susceptibility: voriconazole, liposomal amphotericin B (LAmB) or both. Outcome measures were proportion of correct treatment, survival and serious adverse events.

Results: Implementing *Aspergillus* PCR tests was projected to result in residual treatment-susceptibility mismatches of <5% for a triazole resistance rate up to 20% (using voriconazole). Empiric LAmB outperformed voriconazole at resistance rates higher than 5-20%, depending on PCR use and estimated survival benefits of voriconazole over LAmB. Combination therapy of voriconazole and LAmB performed best at all resistance rates but the advantage over the other strategies should be weighed against the expected increased number of drug related serious adverse events. The advantage of combination therapy over LAmB monotherapy became smaller at higher triazole-resistance rates.

Conclusions: Introduction of current *Aspergillus* PCR tests on BAL-fluid is an effective way to increase the proportion of patients that receive adequate targeted therapy for IA. The results indicate that close monitoring of background resistance rates and of adverse drug events are important to attain the potential benefits of LAmB. The choice of strategy ultimately depends on the probability of triazole-resistance, the availability of PCR and individual patient characteristics.

INTRODUCTION

Invasive aspergillosis (IA) is an opportunistic fungal infection with rising incidence among various patient populations. Patients treated for haematological malignancy with intensive chemotherapy or haematopoietic stem cell transplantation (HSCT) are the population with the highest risk of developing IA and often receive antifungal chemoprophylaxis throughout treatment. Despite the use of chemoprophylaxis, incidence rates in this population remain substantial and IA continues to cause significant morbidity and mortality (1). Developments in applicability of PCR diagnostics as well as the increasing incidence of antifungal resistance worldwide urgently calls for optimization of the strategies for managing IA (2, 3).

Aspergillus triazole resistance rates in Northwestern Europe are reported to be amongst the highest in the world, varying between 8-15% and showing an increasing trend over time. Multiple reports of worldwide emerging triazole-resistance confirm that the problem is expanding on a global scale. This is presumably due to the high mobility of *Aspergillus* spores and increased awareness (3, 4).

When inadequately treated with triazoles, the mortality of patients infected with triazole resistant *Aspergillus spp*. is reported to be high as 88% (5, 6). Hence, triazole resistance will increasingly complicate the efficacy of chemoprophylaxis and therapeutic management of IA and is associated with a higher mortality.

Due to the limited sensitivity of culture with subsequent susceptibility testing, triazole-susceptibility is often unknown, which creates a clinical dilemma. Evidence of superior efficacy of triazoles versus amphotericin B has been demonstrated in the trial by Herbrecht et al. in 2002 (7). Since then, no head-to-head comparisons between voriconazole versus any formulation of amphotericin B have been investigated under randomized conditions. Thus, voriconazole has remained the primary treatment choice in international guidelines (8). However, the risk of treating disease caused by triazole-resistant *Aspergillus* with a triazole could offset the potential survival benefit in the overall population. The importance of initiating the correct treatment as soon as possible is supported by survival data that show that mortality is highest within the first phase of treatment (9-11).

In recent years, polymerase chain reaction (PCR) on bronchoalveolar lavage (BAL)-fluid opened up new possibilities in the diagnosis of IA. In addition to providing a higher sensitivity and specificity in BAL-based diagnostics, this technique is now able to detect triazole resistance on a genetic level by analysis of CYP51-gene mutations. Thereby, phenotypical susceptibility testing on a positive culture is no longer the only way to demonstrate the presence of antifungal resistance (12). Effectively implementing this new strategy facilitates the use of rapid targeted therapy. However, setting up a randomized diagnostic trial using PCR-based diagnostics in a setting of triazole resistance would need a high number of participants and many years to complete.

Hence, our first aim is to combine available data of previous study outcomes and current test characteristics in a simulation model to assess the potential impact of PCR diagnostics and the selective use of voriconazole and liposomal amphotericin B (LAmB) on mortality. We explore three different strategies that reflect the current clinical landscape. The second aim of this study is to explore which information would be most useful to collect to reduce the uncertainties regarding the survival benefit of voriconazole versus LAmB under different resistance rates in a comprehensive model.

DESIGN

Population

The modelling study focused on a population comprised of patients undergoing treatment for a haematological malignancy. The main assumptions were that a clinical suspicion of IA caused by *Aspergillus* fumigatus was present, and a BAL was performed in an attempt to establish the diagnosis. Polyene resistance was presumed to be absent. The population consisted of 1000 patients, a number that a large multicentre study might reach within several years. PCR results were supposed to be available within 48 hours, thus preventing a relevant delay in susceptibility testing.

Strategies

All patients in this population were subjected to six different strategies of diagnosis and treatment. In all six strategies (table 1), patients with proven susceptible IA were treated with voriconazole monotherapy and patients with proven resistance were treated with LAmB monotherapy. The strategies differ in empiric therapy used in case of unknown azole-susceptibility (strategy 1 uses voriconazole (VOR), strategy 2 uses LAmB, and strategy 3 uses a combination of both (COMB)), as well as the use of diagnostic PCR (strategies 1A, 2A, 3A use diagnostics without PRC, whereas strategies 1B, 2B, 3B use PCR for resistance detection).

Table 1: Overview of the diagnostics and treatment used in six different strategies for managing invasive aspergillosis.

Strategy	PCR for resistance detection	demonstrated azole-resistance	demonstrated azole-sensitivity	Unknown Azole-Sensitivity
1A	No	LAmB	Voriconazole	Voriconazole
1B	Yes	LAmB	Voriconazole	Voriconazole
2A	No	LAmB	Voriconazole	LAmB
2B	Yes	LAmB	Voriconazole	LAmB
3A	No	LAmB	Voriconazole	Combination therapy voriconazole + LAmB
3B	Yes	LAmB	Voriconazole	Combination therapy voriconazole + LAmB

Legend: PCR denotes polymerase chain reaction, LAmB liposomal amphotericin B.

Outcome measures

The relevant outcomes were: the proportion of patients with triazole resistant IA that received the correct treatment (i.e. LAmB), and conversely, the percentage with treatment mismatch, as well as the survival and the occurrence of serious adverse events. Given the rarity of LAmB resistance in *Aspergillus* fumigatus, therapy mismatch was defined in this study only as voriconazole in case of triazole resistance. LAmB was considered correct treatment regardless of azole susceptibility. Possible survival disadvantage of LAmB compared to voriconazole in case of azole susceptibility was addressed in the model.

Decision tree

A decision tree that reflects the diagnostic pathway for the six strategies has been constructed (figure 1). The path each simulated patient takes was determined by probabilities for each step in the pathway. If the galactomannan test is negative, a positive result on the *Aspergillus* PCR is highly improbable, and these exceptions were not included in the model (12-14). The outcome of culture is displayed before the outcome of the PCR, although chronologically, the reverse would be true. The possible benefit of earlier diagnosis by PCR was not taken into account. However, the flowchart order of culture and PCR has no effect on the model outcomes. The displayed order demonstrates the added value for PCR in culture negative patients most clearly.

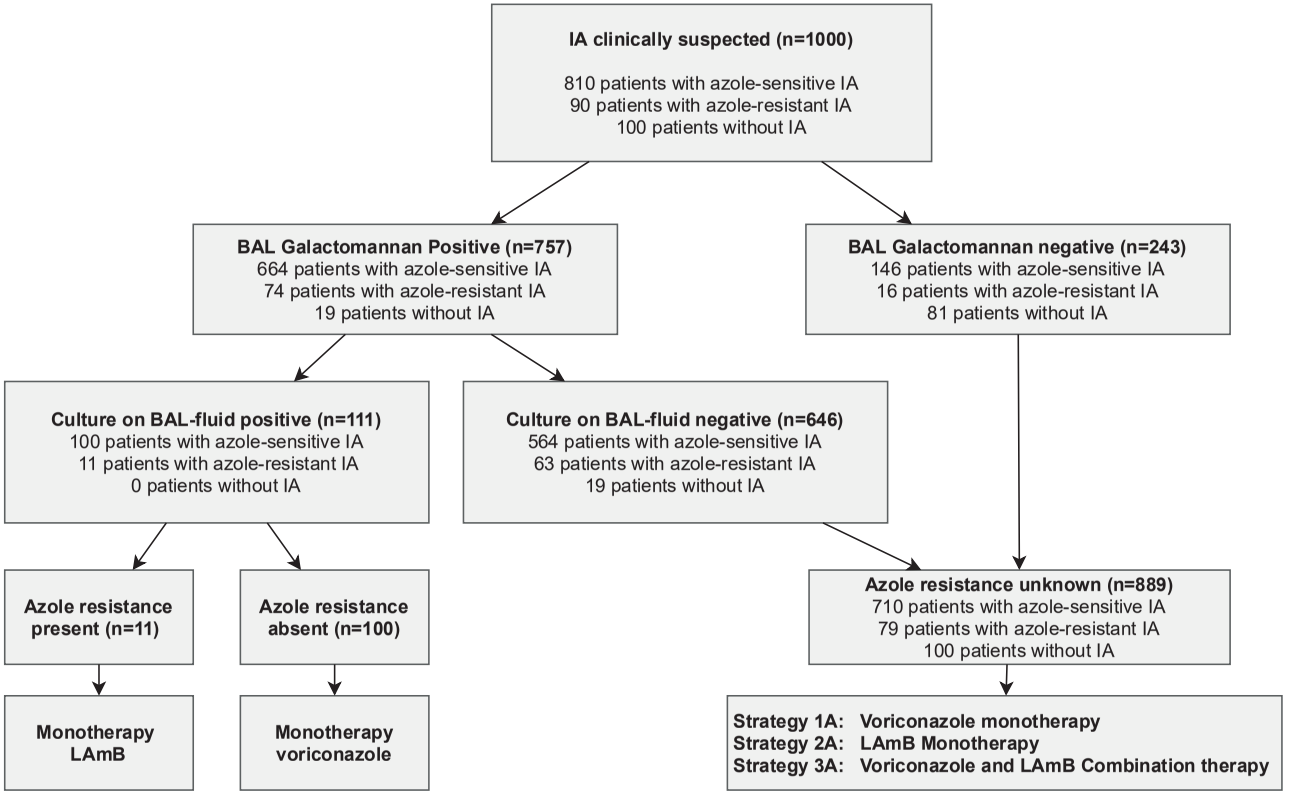
Literature review

To obtain realistic characteristics of the performance of diagnostic tests and the outcome of disease, a literature review was conducted. The values of probabilities for different steps in the diagnostic pathway were extracted from published meta-analyses, systematic reviews or randomized controlled trials. When the values of these probabilities could not be determined precisely from the literature, a sensitivity analysis for this value was used to explore the impact of this uncertainty on the outcome of the simulation model. The sensitivity and specificity values as well as the accuracy of resistance detection was extracted from two recent studies that evaluated PCR techniques in at least 100 clinical cases. Sensitivity of PCR varies widely depending on the DNA isolation and amplification methods and therefore only commercial real-time assays directing CYP51 mutations were included. Notable studies with smaller numbers of included patients show similar values (14, 15).

Parameter values and sensitivity analysis

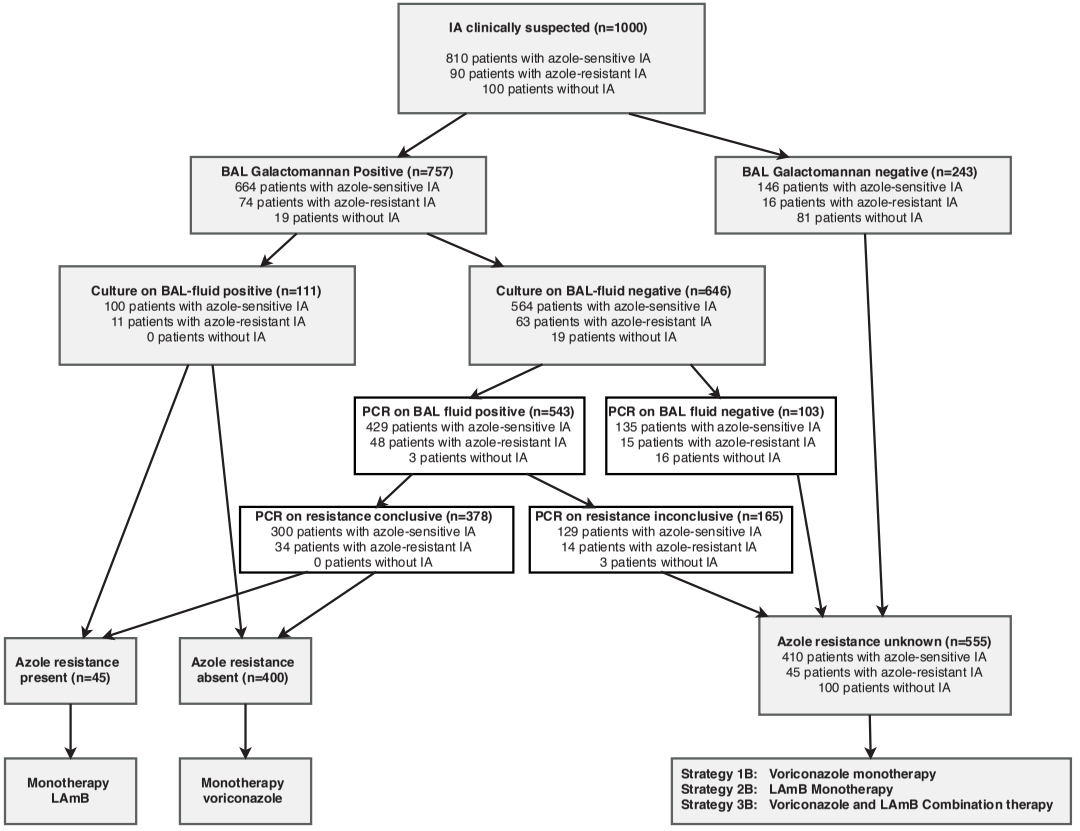
Based on the literature review, the probabilities were set to values as indicated in Table 2. To reflect the uncertainty in the survival between treatment with voriconazole and LAmB, three different scenarios were explored: (1) the mortality of patients treated with LAmB is consistent with the rates of conventional amphotericin-b deoxycholate as extracted from Herbrecht et al. (10) (0.371); (2) the mortality of patients treated with LAmB is consistent with the rates from the AmBiload study (0.280) (11, 16); (3) the mortality of patients treated with LAmB

Figure 1. Treatment flowcharts for the six different treatment strategies
A. Treatment flowchart for all strategies for managing invasive aspergillosis without using a PCR, representing strategy 1A, 2A and 3A



Legend: IA denotes invasive aspergillosis, BAL bronchoalveolar lavage, LAmB liposomal amphotericin B. Patients follow the steps in the flowchart according to the characteristics presented in table 2.

B. Treatment flowchart for all strategies for managing invasive aspergillosis using a PCR on BAL-fluid, representing strategy 1B, 2B and 3B



Legend: IA denotes invasive aspergillosis, BAL bronchoalveolar lavage LAmB liposomal amphotericin B, PCR polymerase chain reaction. Patients follow the steps in the flowchart according to the characteristics presented in table 2.

is estimated to be an aggregate of scenario (1) and (2), set at 0.325. To explore the impact of strategies over a realistic range of triazole resistance rates (2, 3, 6, 17, 18), we varied resistance rates from 5%, increasing in steps of 5% up to a triazole resistance rate of 30%.

Table 2: Overview of literature used to specify different patient, test and treatment characteristics.

Parameter	Literature used	Value
Sensitivity of clinical suspicion	*NA*	NA
Specificity of clinical suspicion	*NA (model assumption)*	0.90
Sensitivity of BAL Gm-assay	*Leeflang[27] 2015*	0.82*
Specificity of BAL Gm-assay	*Leeflang[27] 2015*	0.81*
Sensitivity of culture	*Barton[28] 2013*	0.15 (0.10 -0.58)
Specificity of culture	*Barton[28] 2013*	NA
Sensitivity of PCR	*Chong[12] 2016, Montesinos[13] 2017*	0.76 (0.66-0.86)
Specificity of PCR	*Chong[12] 2016, Montesinos[13] 2017*	0.83 (0.80-0.86)
Probability of successful susceptibility determination by PCR	*Chong[12] 2016*	0.70
VOR 12 week CFR (triazole-sensitive)	*Herbrecht [10] 2002 (updated[10] 2015)*	0.245
VOR 12 week CFR (triazole-resistant)	*Van der Linden 2011, Steinmann [6] 2015*	0.88*
AmB-d 12 week CFR	*Herbrecht [10] 2002 (updated[10] 2015)*	0.371
LAmB 12 week CFR	*Cornely[11] 2007*	0.280
VOR risk of serious AE	*Herbrecht [10] 2002 (updated 2015)*	0.05
LAmB risk of serious AE	*Botero Aguirre[29] 2015*	0.128*

Legend: NA denotes not available; Gm galactomannan; BAL bronchoalveolar lavage; VOR voriconazole; CFR case fatality rate; LAmB liposomal amphotericin B; PCR polymerase chain reaction. Amb-d amphotericin b deoxycholate; AE adverse event. *Study population not limited to haemato-oncological patients but consisting of different immunocompromised patients.

Statistical analysis

STATA (StataCorp. 2012. Statistical Software, Release 12.0) was used to perform all analyses and to construct the graphs. The syntax that was used to build the database and to perform the analyses can be found in the supplemental data (supplement 1, published online).

RESULTS

Literature review and model parameters

The results of the literature review are summarized in table 2. All studies only included patients that were being treated for a haematological malignancy unless stated otherwise. In case of different value parameters extracted from multiple relevant studies, an aggregate mean value has been used. Herbrecht et al. (7, 10) performed the only randomised trial that has investigated

a head-to-head comparison between voriconazole versus a formulation of amphotericin B. However, there is ongoing debate about the applicability of the results in the current clinical landscape (7, 11, 16). Because the study by Herbrecht et al. compared voriconazole with amphotericin B deoxycholate instead of the currently used liposomal formulation, it has been argued that the survival benefit of voriconazole is in fact smaller. The AmbiLOAD trial (11) has provided a randomized study population that has been treated with LAmB. As argued by Denning et al. (16), one could compare the results from both studies and conclude that there is no difference in survival between voriconazole and LAmB.

There was no consistent data that allowed for the estimation of survival of patients with IA primarily treated with both voriconazole and liposomal amphotericin B, survival in strategy 3A and 3B was therefore presumed to be equal to that of voriconazole for a triazole-sensitive IA and to that of LAmB for a triazole-resistant IA. Clinical evidence for an antagonistic or synergistic effect of the combination of an polyene and a triazole is absent (19, 20).

Model outcomes

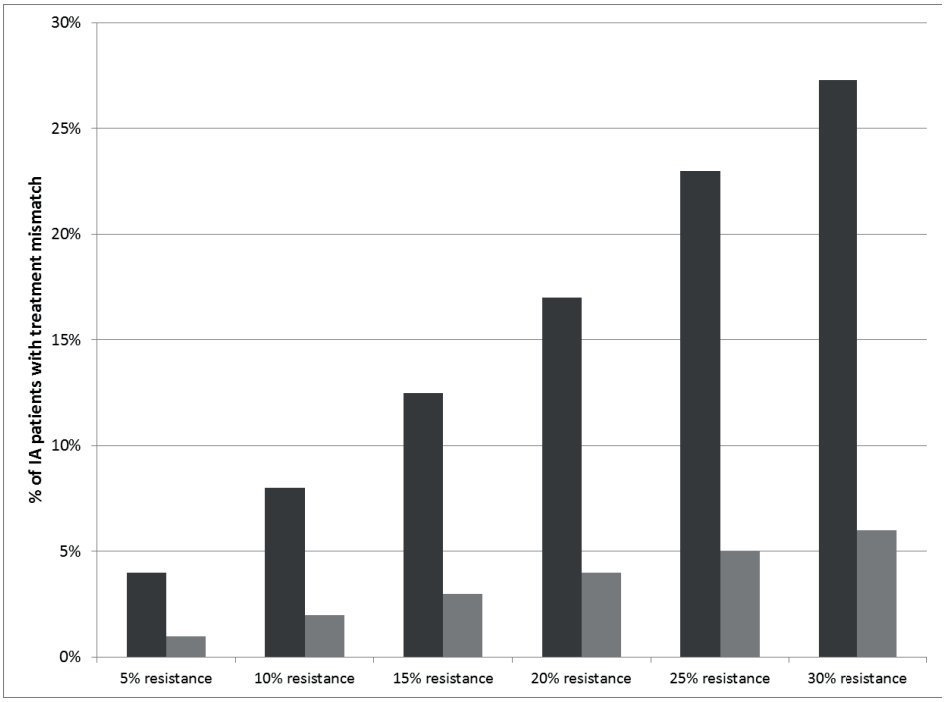
Each of the 1000 patients in the population followed the decision tree for each scenario. Numbers of patients in each step are shown in figure 1. The numbers of patients in each step are based on the parameters presented in table 2. For example, the number of patients with IA that get a positive BAL-galactomannan (664 triazole-sensitive plus 74 triazole-resistant IA patients) is computed as the sensitivity of the BAL-galactomannan test (0.82) multiplied by the total number of patients with IA (810 triazole-sensitive plus 90 triazole-resistant IA patients). The same goes for the patients without IA, using 1 minus the specificity (1 minus 0.81 = 0.19), resulting in 19 patients without IA and a false positive test.

Based on the parameters aggregated in table 2, we have simulated the effects on our primary outcomes: the proportion of patients with triazole resistant IA that received the correct treatment (i.e. LAmB), case fatality rate and the occurrence of serious adverse events.

Correct treatment

Using the targeted strategies in which PCR diagnostics were implemented, more patients received LAmB for a triazole-resistant IA and voriconazole for triazole-sensitive IA. The higher the rate of triazole-resistance, the larger the benefit of the targeted strategy 1B on the decrease of treatment-mismatch (figure 2). If PCR is not used, a linear increase in the number of patients incorrectly treated with voriconazole is expected when resistance rates are rising. Up to a triazole-resistance percentage of 20% of all IA occurrences, this number can be reduced below 5% by implementation of PCR-based triazole-susceptibility testing. Not displayed in this graph are strategy 2A, 2B, 3A and 3B, as these strategies include the use of LAmB in case of unknown triazole sensitivity and will thereby always guarantee adequate treatment of triazole resistant IA.

Figure 2. Triazole-resistant invasive aspergillosis treated with voriconazole in strategy 1A (no PCR) vs 1B (PCR) as a percentage of all patients with invasive aspergillosis.



Legend: VOR denotes voriconazole; PCR polymerase chain reaction; IA invasive aspergillosis. Treatment mismatch is defines as an azole resistant invasive aspergillosis treated with voriconazole. Details of different strategies can be found in table 1.

Survival

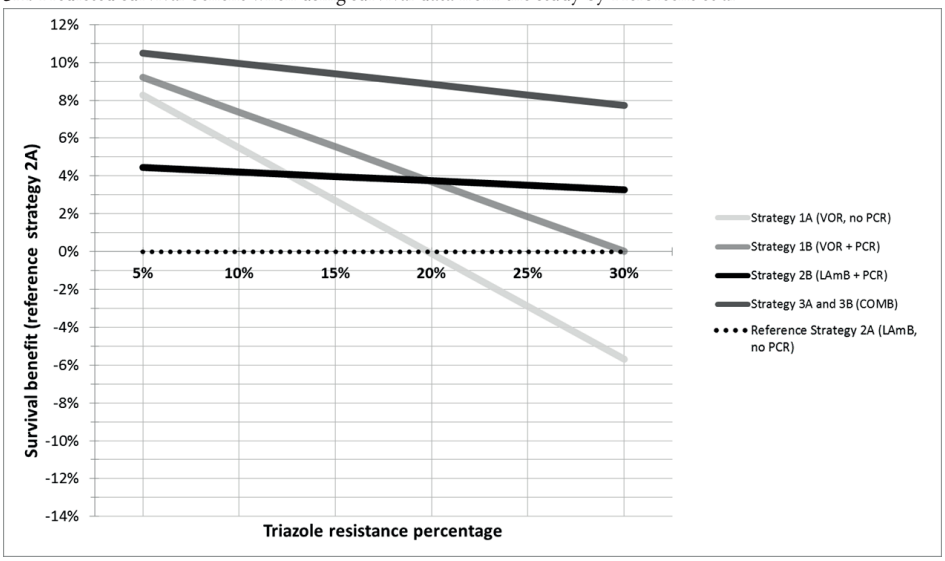
As survival in strategy 2A is almost constant among the different imputed resistance rates (varying less than 0.5% between the outer values), this strategy was most suitable as reference category. The absolute survival benefit of the other strategies when compared to strategy 2A (LAmB in case of unknown triazole-susceptibility, no use of PCR) is displayed in figure 3A-C.

Survival improves in strategy 1B (VOR + PCR) compared to 1A (VOR, no PCR) due to the decreased proportion of patients with triazole-resistant IA who are treated with voriconazole (see also figure 2). The higher the rate of triazole-resistance, the larger the benefit of the PCR diagnostics was in the simulated population.

Strategy 2A and 2B (LAmB) are inferior to strategy 1A and 1B (VOR) at low resistance rates, and only provide better survival if the resistance rates are high enough. Depending on the assumed superiority of VOR over LAmB for azole-susceptible IA, the tipping point of superiority is around 20% (figure 3A, Herbrecht data) to only 5% (figure 3C, AmbiLoad data).

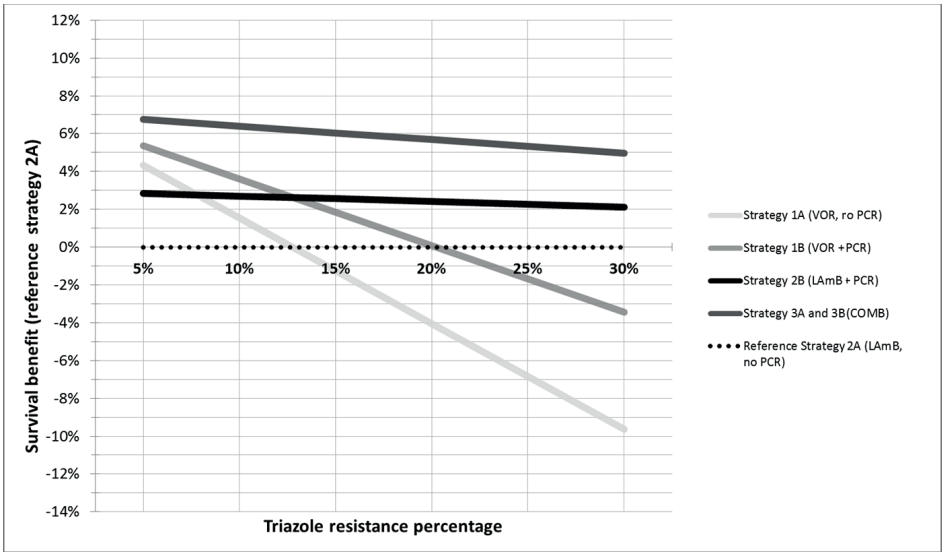
Figure 3. Predicted absolute survival benefit of different clinical strategies compared to strategy 2A (liposomal amphotericin B in case of unknown triazole-susceptibility and no use of PCR resistance detection) in patients with invasive aspergillosis.

3A: Predicted survival benefit when using survival data from the study by Herbrecht et al



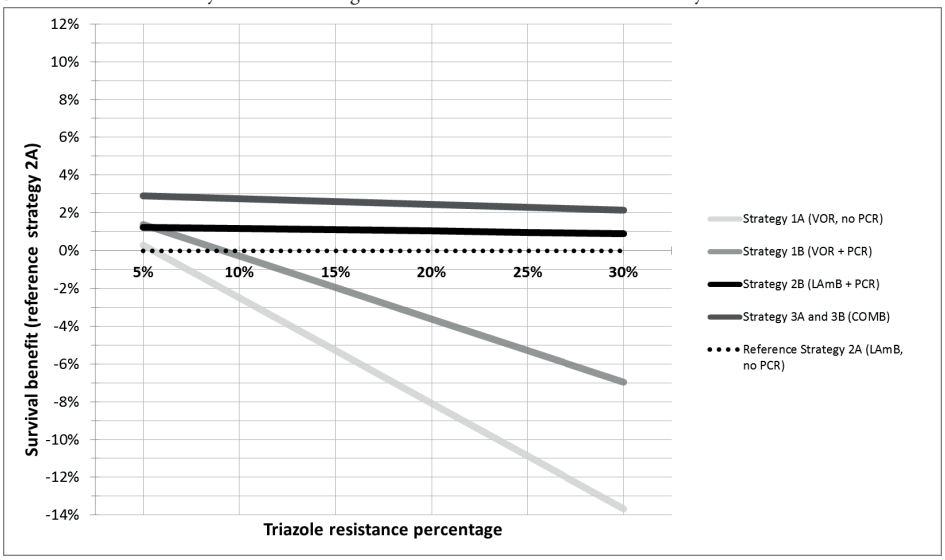
Legend: VOR denotes voriconazole; LAmB liposomal amphotericin B; PCR polymerase chain reaction. Details of different strategies can be found in table 1.

3B: Predicted survival rates when combining survival data from the AmbiLOAD study and the study by Herbrecht et al.



Legend: VOR denotes voriconazole; LAmB liposomal amphotericin B; PCR polymerase chain reaction. Details of different strategies can be found in table 1.

3C: Predicted case fatality rates when using survival data from the AmbiLOAD study



Legend: VOR denotes voriconazole; LAmB liposomal amphotericin B; PCR polymerase chain reaction. Details of different strategies can be found in table 1.

Strategy 3A and 3B (COMB) yield the best survival for all resistance rates. The use of PCR in strategy 3B only benefits the rates of adverse events due to increased use of targeted monotherapy, so no difference between mortality was found between strategy 3A and 3B. Therefore, the results of these strategies are shown as a single line (figure 3A-C).

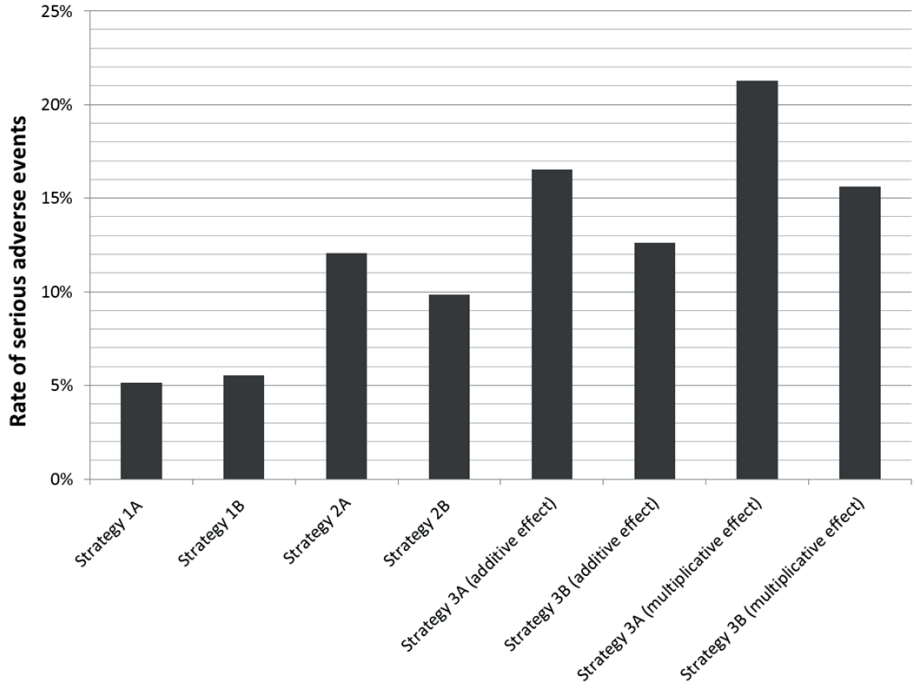
Above 20% resistance rates we found a clear inferiority of strategies that use voriconazole in case of unknown triazole-susceptibility (strategy 1A and 1B); however, the advantage of the other strategies must be weighed against the expected increased serious adverse event rates. Notably, the advantage of combination therapy versus LAmB monotherapy becomes increasingly smaller at higher triazole-resistance rates. At 15% percent resistance, the survival difference between these strategies is around 1.5% percent using only the data from the AmBiLoad trial to calculate survival rates (figure 3C). At lower resistance rates (less than 10%), strategy 1B remained within a range of 3% survival inferiority when compared to combination therapy, even when only the survival data from the AmBiLoad study were used (figure 3A).

Toxicity

Strategies 3A and 3B (COMB) had the highest rates of serious adverse events as they often combine both toxic forms of therapy (figure 4). When comparing strategy 1A and 1B (VOR), patients who were tested with a PCR suffered more nephrotoxicity as more patients are treated with LAmB whereas in strategy 2 and 3, PCR decreased toxicity by reducing unnecessary use of LAmB. We explored both an additive and multiplicative effect of therapy on serious adverse

events. This reveals that the rate of serious adverse events may be even higher if there is a multiplicative effect of therapy on toxicity. Resistance rate increase did not have an important effect on adverse event rates and are not shown in the graph. At most, a 1% difference in adverse event rate was found between the outer values of the imputed resistance rates. The weighing of resistance rates against survival rates are important as the survival benefit is smaller at low resistance rates but the occurrence of adverse events remains relatively stable.

Figure 4: Predicted rates of serious adverse events in six different clinical strategies using both an additive and a multiplicative model to predict outcomes of combination therapy



Legend: Details of different strategies can be found in table 1**.**

DISCUSSION

Summary

Our study provides a comprehensive insight in the strengths and weaknesses of different strategies of antifungal chemotherapy for IA. Introduction of species- and CYP51-gene PCR of BAL-fluid seems to provide an effective way to increase the number of patients that receive targeted therapy for IA. The current limitations in sensitivity and specificity leave around half of all patients in which antifungal sensitivity remains unknown, thus necessitating a well informed choice for this large group of patients. Strategies that incorporate the use of LAmB

in case of unknown triazole-susceptibility are more effective when the background resistance rates are higher and when the true difference of treatment effectiveness between voriconazole and LAmB is smaller. The occurrence of antifungal related serious adverse events is higher in a strategy in which more patients receive LAmB. This holds particularly true for a strategy that combines LAmB and voriconazole, although the exact number of adverse events is hard to quantify due to insufficient data.

Validity of the model assumptions

The performance of PCR in the diagnosis of IA is only recently explored and the experience with the diagnostic value in clinical practice is limited (12). The difference between the A and B variants of the strategies (with or without PCR) is largely dependent on the data from a few studies published after the introduction of this diagnostic method (12-14). More recent findings suggest the initial findings may be too optimistic (21). On the other hand, research devoted to the combination of PCR with other diagnostic assays also show promising results (22-24). Of note, the techniques that were included in the literature review only cover a single resistance locus; changes in epidemiology of the resistance mechanisms could potentially decrease the benefit of PCR for susceptibility testing. Moreover, these studies were not powered to provide an estimate for the sensitivity of the PCR for the detection of resistance.

Another important factor in the model is the a priori chance of the presence of a clinical significant fungal infection in a patient with a positive HR-CT scan. Our results are in particular dependent on this number; if this chance is lower, a lot of patients would unnecessarily be exposed to the toxic effects of LAmB or combination therapy and the survival differences would be smaller. It is difficult to provide a reliable estimate of this chance, as the positive HR-CT itself justifies the diagnosis of a possible IA in an appropriate host. Our only source could be the results from autopsy studies (25, 26). The absence of IA at an autopsy does not rule out the absence of IA at the moment of the initiation of treatment however. Hence, using data from autopsy studies would underestimate this probability. In clinical practice, it is assumed that a positive HR-CT scan in absence of more plausible differential diagnostic entities is a fairly certain marker of the presence of disease. Therefore, for the purpose of our study, a probability of 0.90 has been implemented in the model.

It should be noted that the numbers on which the estimates of resistance percentages are based on, are mostly derived from data of probable and proven IA, and could therefore be an overestimation of the overall resistance percentage. The difference in resistance rates between continents, regions and even individual hospitals are an important aspect in the interpretation of our study results for a policy in clinical practice. Additionally, polyene resistance is not taken into account. Hospitals that are experiencing a substantial burden of polyene resistant species should expect that the benefits of LAmB are lower than in the simulated population.

We have incorporated as many relevant factors as possible in the model in order to take into account all aspects of the treatment landscape in which the clinical problem takes place.

However, one important factor that is worth mentioning is the absence of a strategy that incorporates the use of echinocandins. Several studies are available on the incorporation of echinocandins in the treatment of IA. It is either used as standard or salvage therapy, as monotherapy or used in conjunction with a triazole or LAmB (27-29). Because these strategies are very diverse and are usually recommended as salvage therapy in international guidelines (8, 30), these strategies were not taken into account in our model.

Strengths and limitations

The strength of our study is the synthesis of evidence present in the current literature. Six different treatment strategies were compared at a range of resistance rates and alternative scenarios for therapy effectiveness. This allows researchers to select those study results relevant to the resistance rates in the population of interest, and this will provide a rationale for discussing an appropriate treatment strategy in their institution.

Our findings open perspectives for further research that will further support clinical decision making. First, it is possible to extend the scope by including relevant information on associated morbidity, quality of life and the costs of treatment and care. This would require reliable results on morbidity, quality of life and costs, and on the relation between IA, antifungal treatment and risk factors for invasive fungal disease. In absence of these reliable results, we have limited our study to treatment options. Second, it is possible to include alternative tests as they come available in the future to keep the results relevant in the ever-changing clinical landscape.

The main strength, as with all simulation studies, is the identification of those parameter values that are most valuable to get more accurate estimates of the impact of treatment. In our study, one of the most valuable parameters is the survival benefit of voriconazole as compared to LAmB. Only one large trial, conducted more than 15 years ago, has compared voriconazole directly to conventional amphotericin B. More recent research (11, 16) suggests that the difference on survival between the two therapies might not be as large as that observed in the study by Herbrecht et al. (10). To address this uncertainty, we have used three different scenarios of relative therapy effectiveness. This way, the validity of the model remains assured within each background assumption of this difference. Another parameter value that would be very informative is the rate of adverse events in combining voriconazole and LAmB use (strategies 3A and 3B). Experience with this strategy is very limited in clinical practice and it is not known if a synergistic or antagonistic antifungal effect exists when combining the two drugs (19, 20). Reversely, this also holds true for a potential interactive effect of the occurrence of serious adverse events (20, 31). The impact of the recent introduction of isavuconazole for the treatment of IA is not addressed by the model. As the first experience with this drug shows a potential effect in reduction of adverse events, implementing this could further increase the benefit of the triazole-class of antifungals over LAmB with regard to drug-related adverse events. Consequently, within the setting of combination therapy of LAmB and a triazole, isavuconazole could potentially remove some of the disadvantages of combining two antifungals

with regard to interactions and toxicity. Evidence suggests that hepatobiliary adverse events, as well as neurological, skin and eye disorders, are less common when using isavuconazole when compared to voriconazole. No effect in reducing mortality was found however. (32, 33)

Conclusions

The choice of the best strategy is largely dependent on the rate of triazole resistance. Among all modelled scenarios, strategies that combine voriconazole and LAmB yield superior survival. However, both lower resistance rates and lower difference in therapy effectiveness between the two classes of antifungals reduce the actual benefit of this strategy when compared to a strategy with monotherapy combined with PCR, while the high rate of expected adverse events remains constant. Implementation of resistance detection with PCR could reduce the adverse events rates if the patients switch to adequate monotherapy following conclusive results in susceptibility testing.

PCR may increase survival in settings where empiric voriconazole is used and may aid in reducing toxicity in settings with empiric LAmB. When estimating the survival benefit of voriconazole versus LAmB by combining the data from the AmbiLOAD (11) and the study by Herbrecht et al. (10), the percentage from which superiority of LAmB is achieved lies between 10% and 15%. However, therapy tailored toward the individual patient should always be pursued. For example, pre-existing nephropathy could discourage the clinician to treat with LAmB, or prolonged triazole exposure through prophylaxis could discourage treatment with voriconazole. Furthermore, clinical risk factors and co-morbidities could change the parameters on which our model is based, and subsequently the expected outcomes.

The model clearly shows that introduction of currently available commercial *Aspergillus* PCR tests on BAL-fluid is an effective way to increase the proportion of patients that receive targeted therapy for IA to obtain the optimal outcomes. Furthermore, it is apparent that close monitoring of background resistance rates and of adverse drug events are important to warrant that the expected benefits of LAmB at higher triazole resistance rates are actually realized.

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