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Managing invasive aspergillosis in haematological patients in the era of resistance polymerase chain reaction 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 broncho-alveolar lavage (BAL) fluid allow for detection of triazole resistance at a genetic level, which has 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: A decision-analytic modelling study was performed based on epidemiological data of IA, extended with estimated dynamics of resistance rates and treatment effectiveness. Six clinical strategies were compared that differ in use of PCR diagnostics (used vs 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 >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 targeted therapy for IA. The results indicate that close monitoring of background resistance rates and 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.

1. 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 are at 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 polymerase chain reaction (PCR) diagnostics as well as the increasing incidence of antifungal resistance worldwide mean that there is an urgent need for optimization of the strategies for managing IA [2,3].

Aspergillus triazole resistance rates in north-western Europe are reported to be amongst the highest in the world, varying between 8% and 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

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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

PCR, polymerase chain reaction; LAmB, liposomal amphotericin B.

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 as high as 88% [5,6]. Hence, triazole resistance will increasingly complicate the efficacy of chemoprophylaxis and therapeutic management of IA, and is associated with higher mortality.

Due to the limited sensitivity of culture with subsequent susceptibility testing, triazole susceptibility is often unknown, which creates a clinical dilemma. In 2002, Herbrecht et al. [7] reported the superior efficacy of triazoles compared with amphotericin B. Since then, no head-to-head comparisons of voriconazole with 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 which show that mortality is highest within the first phase of treatment [9–11].

In recent years, PCR on broncho-alveolar lavage (BAL) fluid has opened up new possibilities in the diagnosis of IA. In addition to providing higher sensitivity and specificity in BAL-based diagnostics, this technique is now able to detect triazole resistance at a genetic level by analysis of *CYP51* gene mutations. Therefore, a positive culture is no longer the only way to demonstrate the presence of resistance [12]. Effective implementation of 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.

As such, the primary aim of this study was 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 liposoml amphotericin B (LAmB) on mortality. Three different strategies that reflect the current clinical landscape were explored. The secondary aim of this study was to explore which information would be most useful to collect to reduce uncertainties regarding the survival benefit of voriconazole vs LAmB under different resistance rates in a comprehensive model.

2. Design

2.1. Population

The modelling study focused on patients undergoing treatment for a haematological malignancy. The main assumptions were that a clinical suspicion of IA caused by *Aspergillus fumigatus* was present, and 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 h, thus preventing a relevant delay in susceptibility testing.

2.2. 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 differed in empiric therapy used in the case of unknown azole susceptibility (Strategy 1 used voriconazole, Strategy 2 used LAmB, and Strategy 3 used both), as well as the use of diagnostic PCR (Strategies 1A, 2A and 3A used diagnostics without PCR, whereas Strategies 1B, 2B and 3B used PCR for the detection of resistance).

2.3. Outcome measures

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

2.4. Decision tree

A decision tree that reflects the diagnostic pathway for the six strategies was constructed (Fig. 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 most clearly the added value for PCR in culture-negative patients.

2.5. 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 and 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 were 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].

2.6. 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 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]; and (3) the mortality of patients treated with LAmB is estimated to be an average of Scenarios 1 and 2, set at 0.325. To explore the impact of strategies over a realistic range of resistance rates [2,3,6,17,18], resistance rates were varied from 5%, increasing in steps of 5% up to a resistance rate of 30%.

2.7. Statistical analysis

STATA Release 12.0 (StataCorp, College Station, TX, USA) 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 online supplementary material.

3. Results

3.1. 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 the case of different value parameters extracted from multiple relevant studies, an aggregate mean value was used. Herbrecht et al. [7,10] performed the only randomized trial that has investigated a head-to-head comparison between voriconazole and a formulation of amphotericin B. However, there is ongoing debate about the applicability of the results in the current clinical landscape [7,11,16]. As 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] provided a randomized study population that was 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 were no consistent data that allowed for the estimation of survival of patients with IA primarily treated with both voriconazole and LAmB B; survival in Strategies 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

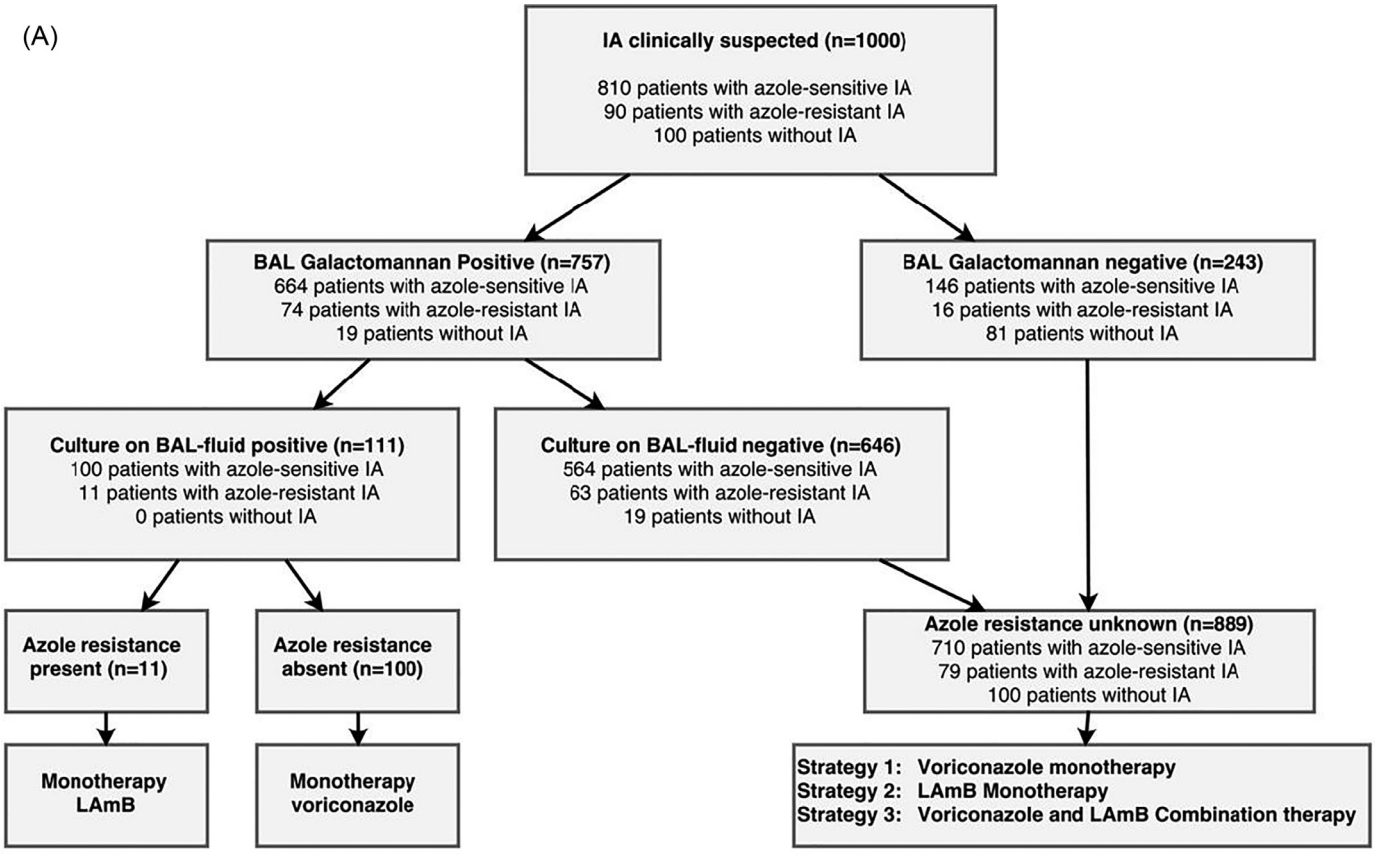


Fig. 1. Treatment flowcharts for the six different treatment strategies. (A) Treatment flowchart for all strategies for managing invasive aspergillosis (IA) without using polymerase chain reaction (PCR), representing Strategies 1A, 2A and 3A. (B) Treatment flowchart for all strategies for managing IA using PCR on broncho-alveolar lavage (BAL) fluid, representing Strategies 1B, 2B and 3B. LAmB, liposomal amphotericin B. Patients follow the steps in the flowchart according to the characteristics presented in Table 2.

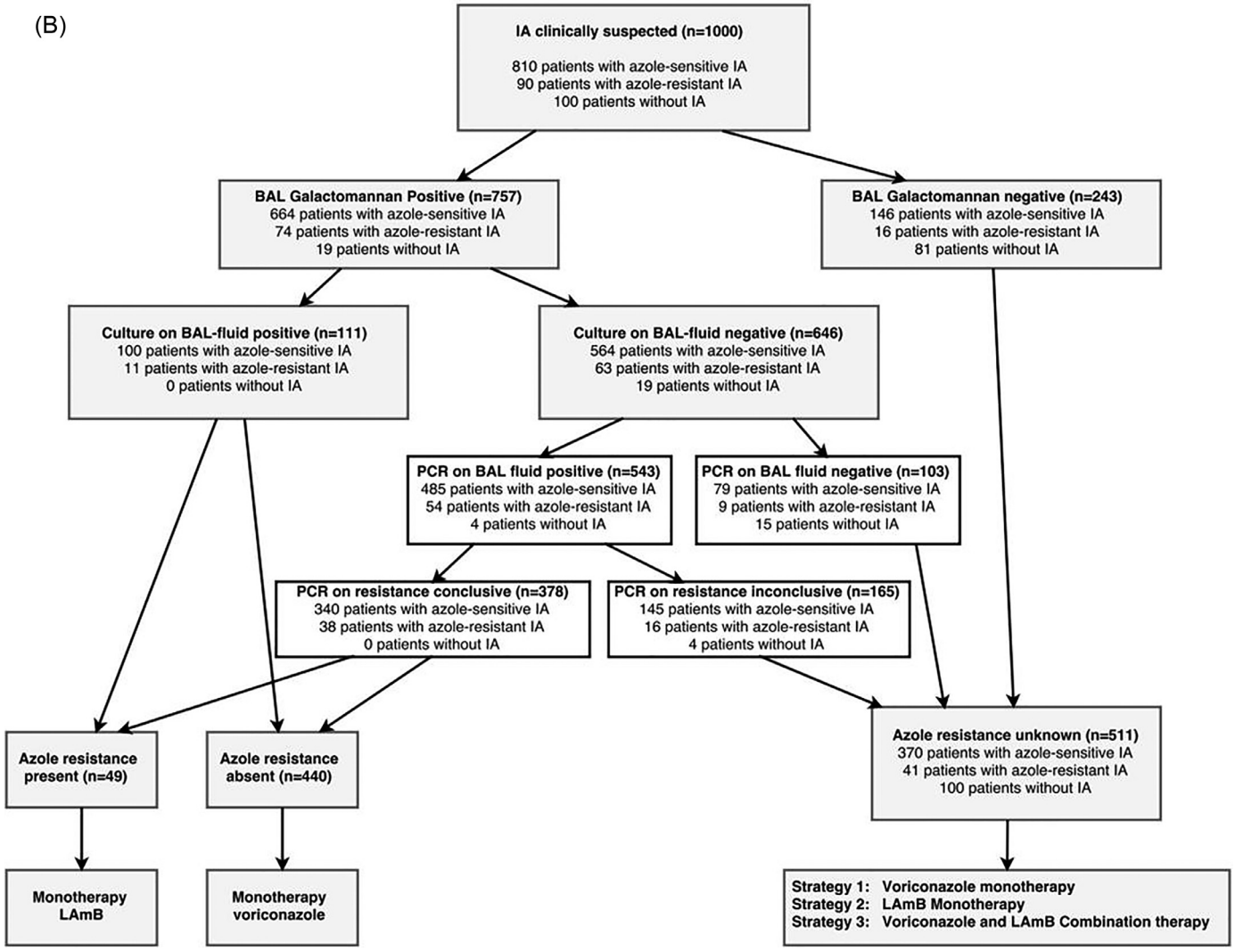


Fig. 1. Continued

IA. Clinical evidence for an antagonistic or synergistic effect of the combination of a polyene and a triazole is lacking [19,20].

3.2. Model outcomes

Each of the 1000 patients in the population followed the decision tree for each scenario. The numbers of patients in each step are shown in Fig. 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 with a positive BAL-galactomannan result (664 triazole-sensitive plus 74 triazole-resistant IA patients) was 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 applies for the patients without IA, using 1 minus the specificity (1 - 0.81 = 0.19), resulting in 19 patients without IA and a false-positive test.

Based on the parameters aggregated in Table 2, the effects on the primary outcomes were simulated, i.e. the proportion of patients with triazole-resistant aspergillosis that received the correct treatment (i.e. LAmB), the case fatality rate and the occurrence of serious adverse events.

3.3. Correct treatment

Using the targeted strategies in which PCR diagnostics were implemented, more patients received LAmB for triazole-resistant IA and voriconazole for triazole-sensitive IA. The higher the rate of triazole resistance, the greater the benefit of Strategy 1B on the decrease in treatment mismatch (Fig. 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 to <5% by implementation of PCR-based triazole susceptibility testing. Not displayed in this figure are Strategies 2A, 2B, 3A and 3B, as these strategies include the use of LAmB in the case of unknown triazole sensitivity and will thereby always guarantee adequate treatment of triazole-resistant IA.

3.4. Survival

As survival in Strategy 2A is almost constant among the different imputed resistance rates (varying by <0.5% between the outer values), this strategy was most suitable as the reference category. The absolute survival benefits of the other strategies when compared with Strategy 2A (LAmB in the case of unknown triazole susceptibility, no use of PCR) are displayed in Fig. 3A–C.

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 [31] 2015	0.82[a]
Specificity of BAL Gm assay	Leeflang [31] 2015	0.81[a]
Sensitivity of culture	Barton [32] 2013	0.15 (0.10–0.58)
Specificity of culture	Barton [32] 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 2015 [10])	0.245
VOR 12-week CFR (triazole-resistant)	Van der Linden 2011, Steinmann [6] 2015	0.88[a]
AmB-d-12 week CFR	Herbrecht [10] 2002 (updated 2015 [10])	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 [33] 2015	0.128[a]

NA, not available; Gm, galactomannan; BAL, broncho-alveolar lavage; VOR, voriconazole; CFR, case fatality rate; LAmB, liposomal amphotericin B; PCR, polymerase chain reaction; Amb-d, Amphotericin b deoxycholate; AE, adverse event.
[a] Study population not limited to haemato-oncological patients but consisting of different immunocompromised patients.

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

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

Strategies 3A and 3B (combination therapy) 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 in mortality was found between Strategies 3A and 3B. Therefore, the results of these strategies are shown as a single line (Fig. 3A–C).

Above 20% resistance rates, a clear inferiority of strategies that use voriconazole in the case of unknown triazole susceptibility was found (Strategies 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 compared with LAmB monotherapy becomes increasingly smaller at higher triazole resistance rates. At 15% resistance, the

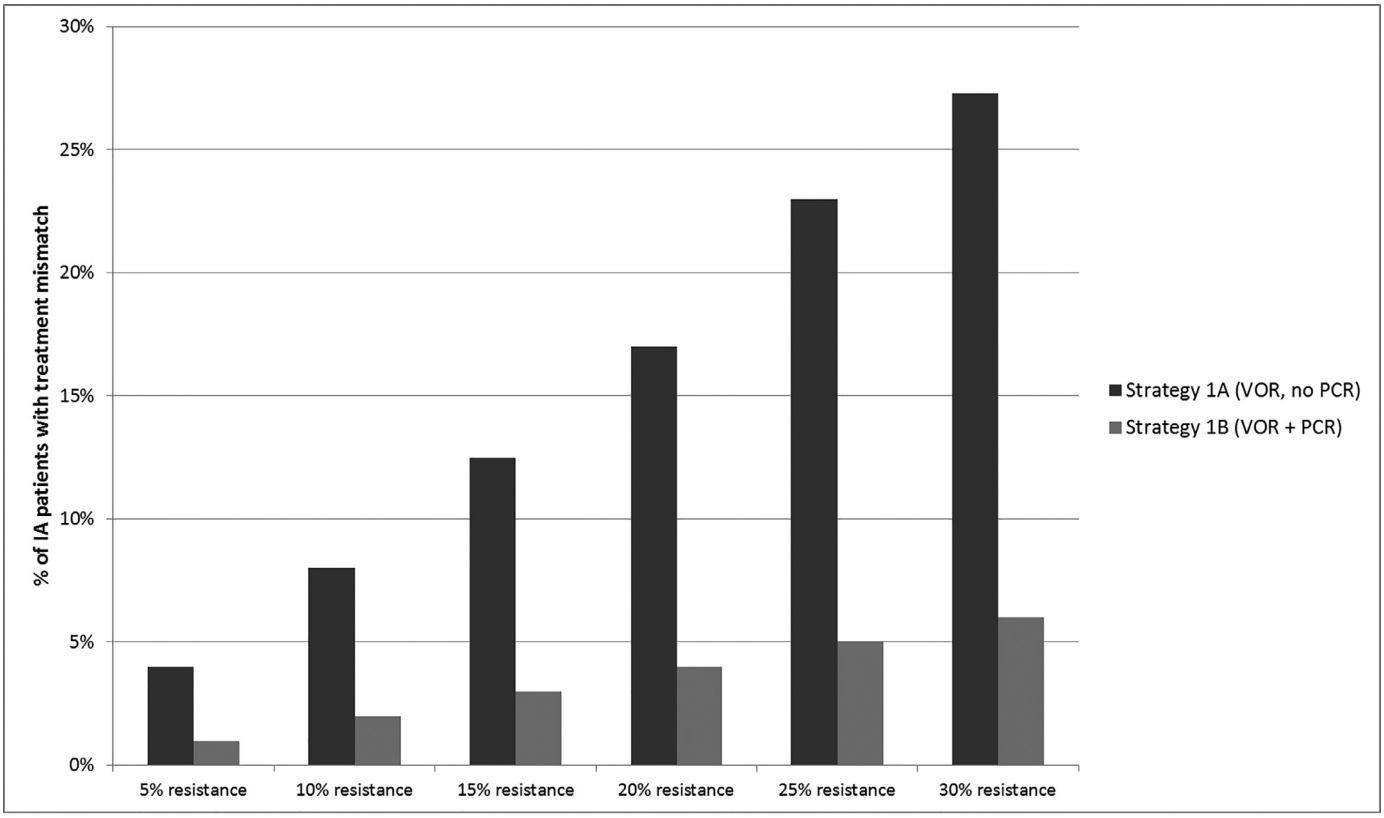
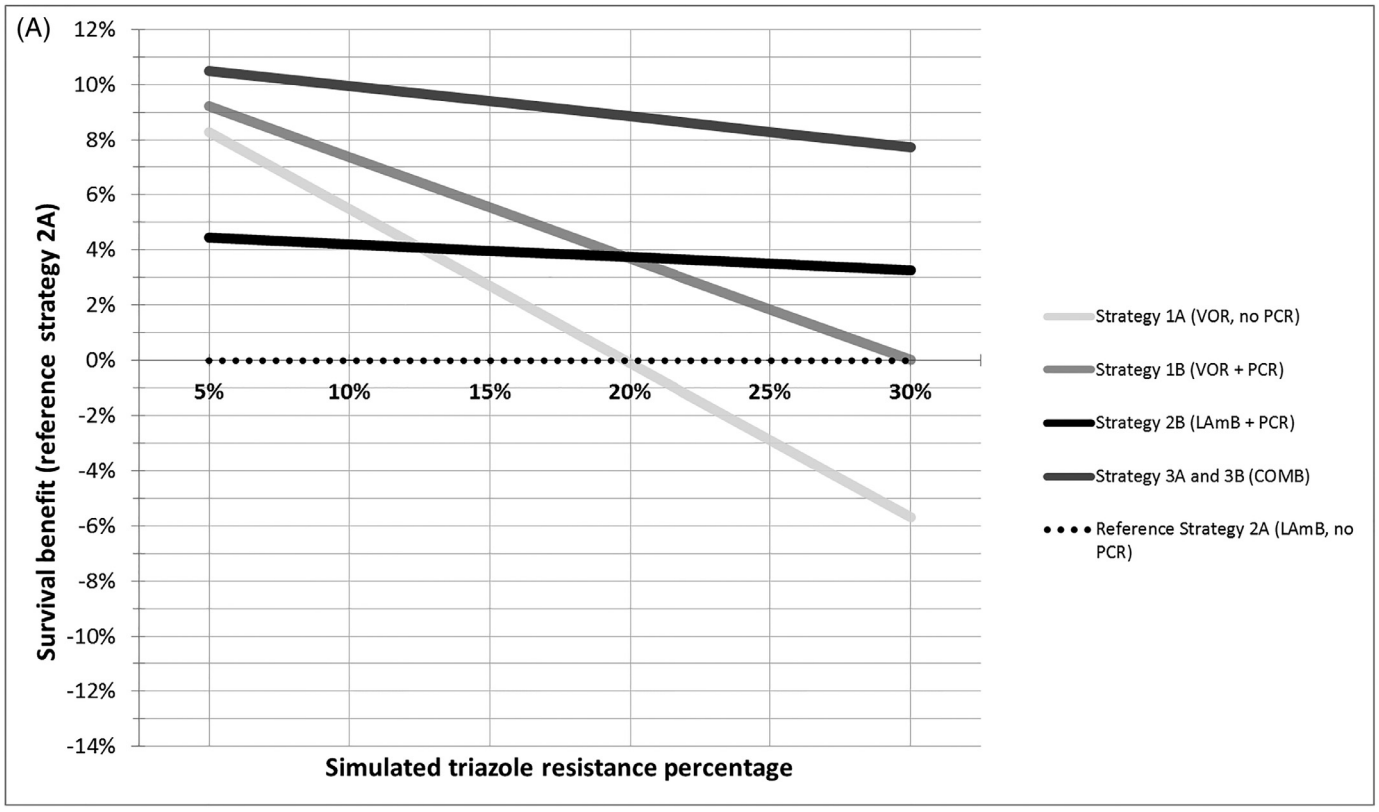


Fig. 2. Triazole-resistant invasive aspergillosis (IA) treated with voriconazole (VOR) in Strategy 1A [no polymerase chain reaction (PCR)] vs Strategy 1B (PCR) as a percentage of all patients with invasive aspergillosis. Treatment mismatch is defined as azole-resistant IA treated with VOR. Details of different strategies can be found in Table 1.



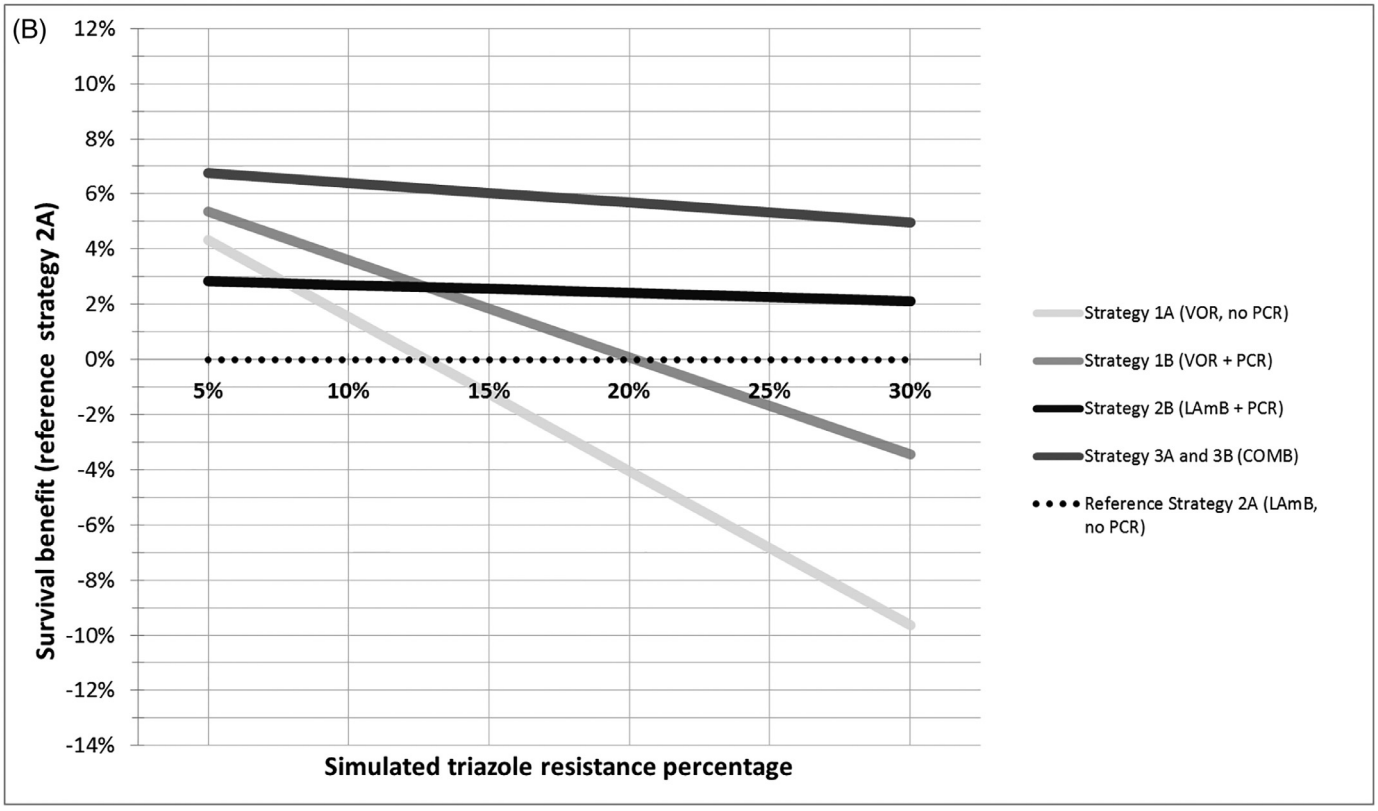


Fig. 3. Predicted absolute survival benefit of different clinical strategies compared with Strategy 2A [liposomal amphotericin B (LAmB) in case of unknown triazole susceptibility and no use of polymerase chain reaction (PCR) resistance detection] in patients with invasive aspergillosis. (A) Predicted survival benefit when using survival data from the study by Herbrecht et al. (B) Predicted survival rates when combining survival data from the AmbiLOAD study and the study by Herbrecht et al. (C) Predicted survival rates when using survival data from the AmbiLOAD study. VOR, voriconazole; COMB, combination therapy (VOR + LAmB). Details of different strategies can be found in Table 1.

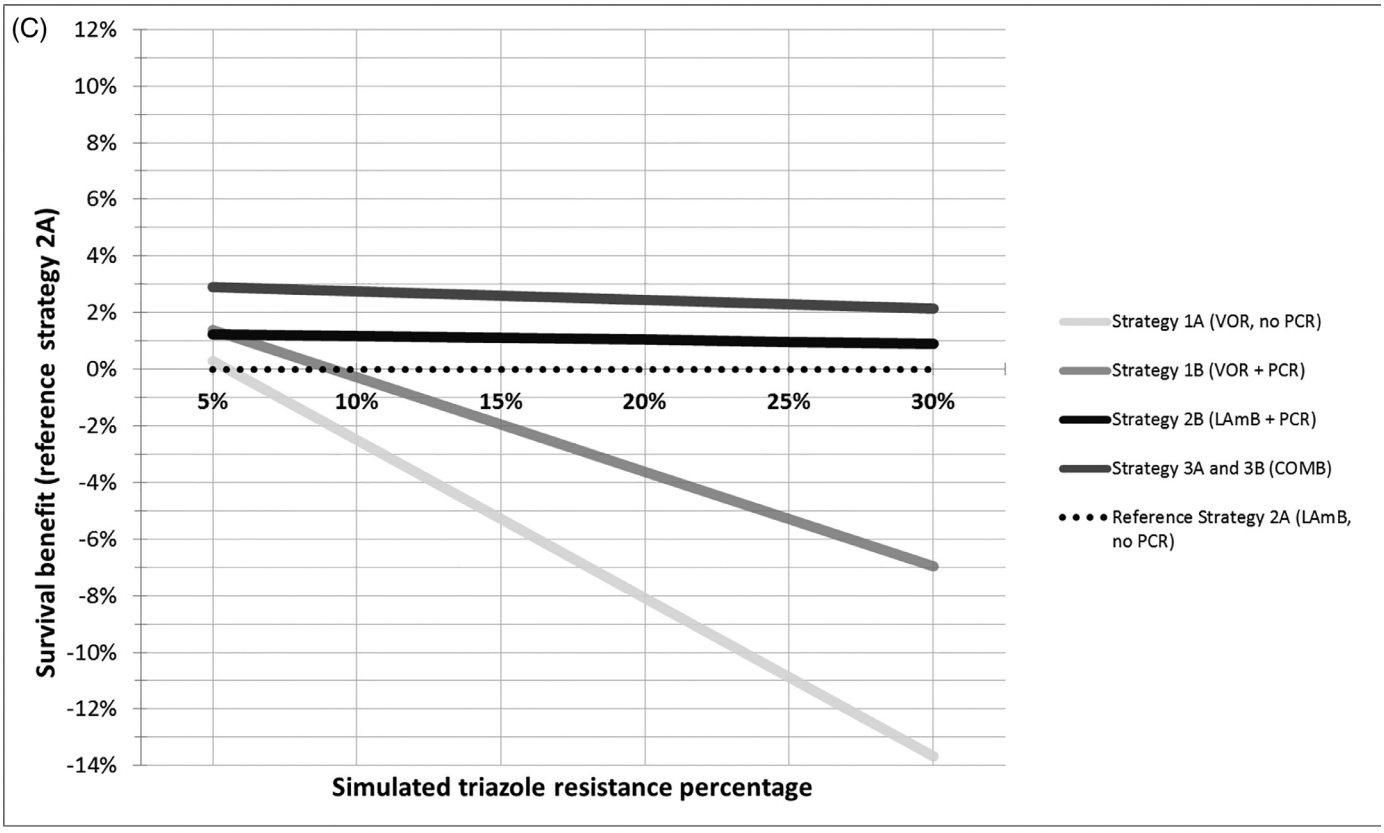


Fig. 3. Continued

survival difference between these strategies is approximately 1.5% using the data from the AmBiLoad trial alone to calculate survival rates (Fig. 3C). At lower resistance rates (<10%), Strategy 1B remained within a range of 3% survival inferiority compared with combination therapy, even when the survival data from the AmBiLoad study alone were used (Fig. 3A).

3.5. Toxicity

Strategies 3A and 3B (combination therapy) had the highest rates of serious adverse events, as they often combine both toxic forms of therapy (Fig. 4). When comparing Strategies 1A and 1B (voriconazole), patients who were tested with a PCR suffered more nephrotoxicity as more patients are treated with LAmB, whereas in Strategies 2 and 3, PCR decreased toxicity by reducing unnecessary use of LAmB. This study 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 is 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.

4. Discussion

4.1. Summary

This study provides a comprehensive insight into 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 result in antifungal sensitivity remaining unknown in approximately half of all patients, thus necessitating a well-informed choice for this large group of patients. Strategies that incorporate the use of LAmB in cases of unknown triazole susceptibility are more effective when the background resistance rates are higher and when the true difference in treatment effectiveness between voriconazole and LAmB is smaller. The occurrence of antifungal-related serious adverse events is higher in a strategy where more patients receive LAmB. This holds particularly true for a strategy that combines LAmB and voriconazole, although the exact number is difficult to quantify due to insufficient data.

4.2. Validity of the model assumptions

The performance of PCR in the diagnosis of IA has only been explored recently, and 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 that the initial findings may be too optimistic [21]. On the other hand, research devoted to the combination of PCR with other diagnostic assays also shows 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 dilute the results of the present study. Moreover, these studies were not powered to provide an estimate for the sensitivity of PCR for the detection of resistance.

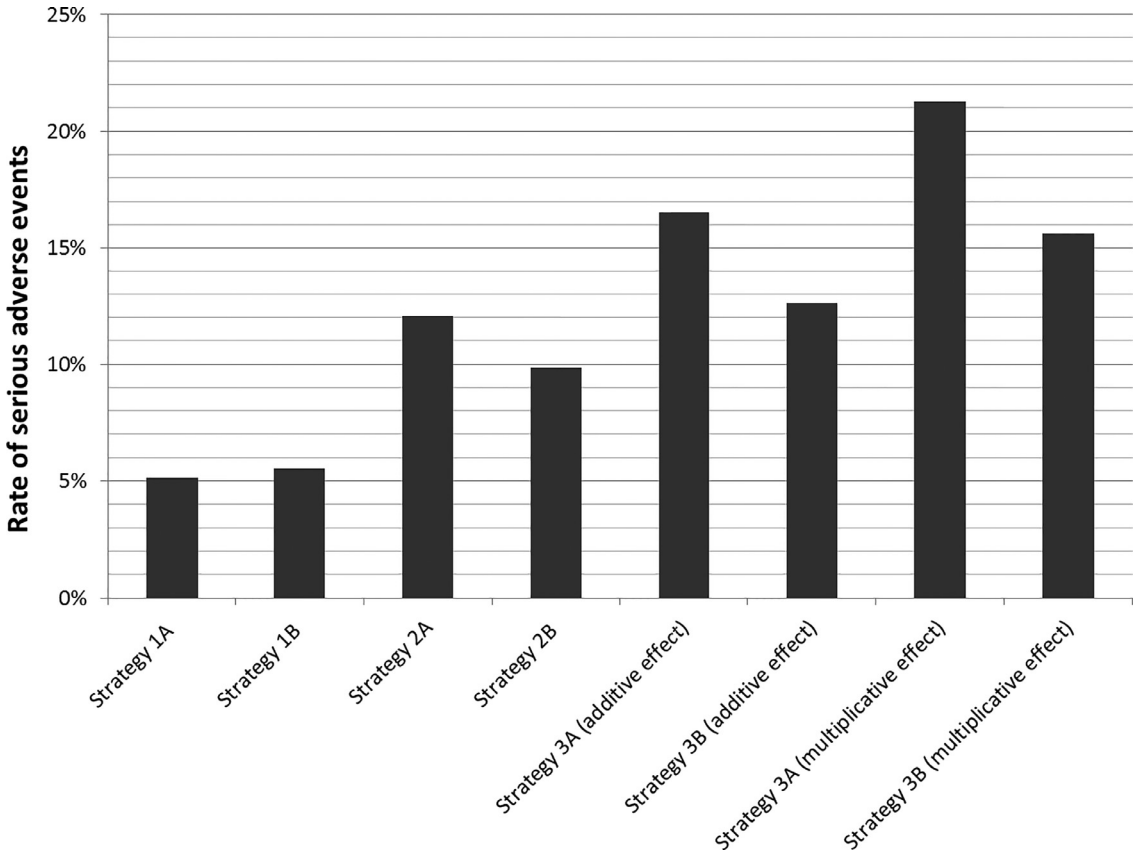


Fig. 4. Predicted rates of serious adverse events in six different clinical strategies using both an additive and a multiplicative model to predict outcomes of combination therapy. Details of different strategies can be found in Table 1.

Another important factor in the model is the a priori chance of the presence of a clinically significant fungal infection in a patient with a positive high-resolution computed tomography (HR-CT) scan. These results are particularly dependent on this number; if this chance is lower, many patients would be exposed unnecessarily 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 scan itself justifies the diagnosis of possible IA in an appropriate host. The only source could be the results from autopsy studies [25,26]. However, the absence of IA at an autopsy does not rule out the absence of IA at the initiation of treatment. Hence, using data from autopsy studies would underestimate this probability. In clinical practice, it is assumed that a positive HR-CT scan in the absence of more plausible differential diagnostic entities is a fairly certain marker of the presence of disease. Therefore, for the purpose of the present 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 are mainly derived from data of probable and proven IA, and could therefore be an overestimate of the overall resistance percentage. Differences in resistance rates between continents, regions and even individual hospitals are an important aspect in the interpretation of the 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 the benefits of LAmB to be lower than in the simulated population.

This study has incorporated as many relevant factors as possible into the model in order to consider 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. They are either used as standard or salvage therapy, as monotherapy or in conjunction with a triazole or LAmB [27–29]. As these strategies are very diverse and are usually recommended as salvage therapy in international guidelines [8,30], these strategies were not considered in the study model.

4.3. Strengths and limitations

A strength of this study is the synthesis of evidence present in the current literature. Six different treatment strategies were compared with a range of resistance rates and alternative scenarios for therapy effectiveness. This allows researchers to select the 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.

These 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 the absence of such reliable results, this study has been limited 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 of this study, as with all simulation studies, is the identification of those parameter values that are most valuable to gain more accurate estimates of the impact of treatment.

In this study, this is the survival benefit of voriconazole compared with LAmB. Only one large trial, conducted more than 15 years ago, has compared voriconazole directly with conventional amphotericin B. More recent research [11,16] suggests that the difference in survival between the two therapies might not be as large as that observed in the study by Herbrecht et al. [10]. Three different scenarios of relative therapy effectiveness have been used to address this uncertainty. 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 for the combination of voriconazole and LAmB (Strategies 3A and 3B). Experience with this combination 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 in the clinical landscape is not addressed by the model. As the first experience with this drug shows a potential reduction of adverse events, implementing this could further increase the benefit of the triazole class of antifungals over LAmB formulations 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 compared with voriconazole. However, no effect in reducing mortality was found [32,33].

5. 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 compared with a strategy with monotherapy combined with PCR, while the high rate of expected adverse events remains constant.

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 compared with LAmB by combining the data from the AmbiLOAD study [11] and the study by Herbrecht et al. [10], the percentage in which LAmB is found to be superior lies between 10% and 15%. However, therapy tailored towards 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 the 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 adverse drug events are important to ensure that the expected benefits of LAmB at higher triazole resistance rates are actually realized.

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Competing interests

None.

Ethical approval

Not applicable.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.021.

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