Cost-effectiveness of different strategies for treating invasive aspergillosis in hematopoietic stem cell transplant recipients using a Markov model

A Research report

Marco Wouters (457037)

Supervisor: Hans Severens

Erasmus University Rotterdam

Master thesis: Health Economics

24-12-2018

Abstract

Objectives: Hematopoietic stem cell transplant recipients have a 10% probability of developing invasive aspergillosis, which is a serious fungal infection with a high mortality. Several cost-effectiveness studies have been performed regarding the treatment of invasive aspergillosis in this particular patient population. Those studies use a decision tree as their model. However, an important disadvantage is that time is not explicitly incorporated in those models. Markov models, in contrary, do have this property which should make them better suited to represent the real-life situation. The objective of this study is twofold. First, it will assess the feasibility and additional value of using a Markov model (and thereby explicitly incorporating time) over a decision tree. Second, it will assess the cost-effectiveness of the different strategies in treating hematopoietic stem cell transplant recipients with invasive aspergillosis, explicitly considering that patients can switch at any time between health states.

Methods: This study is based on the study of Ament et al. (2007) and since no individual patient data was available, data from their study had to be used. The study population consists of adult hematopoietic stem cell transplant recipients with proven or probable invasive aspergillosis. Five treatment strategies are compared which included Voriconazole, Caspofungin, Desoxycholate amphotericin B and Liposomal amphotericin B. The study is performed from the perspective of the health care purchaser. The Markov model consists of cycles of 1 day, with a time horizon of 5 years. At any time, patients in the study were in either of the following five health states: first-line treatment, second-line treatment, other licensed antifungal treatment (OLAT), finished antifungal treatment, death. The main outcomes are incremental cost-effectiveness ratio's and net monetary benefits with a threshold of 50.000 euro per life year gained.

Results: It is feasible to build a Markov model for this particular patient population. However, along the process, some problems emerged, which involved negative patient values, incorporating costs, and choosing the right distribution for the survival analysis. In our model Voriconazole + Desoxycholate, amphotericin B was dominant over all strategies except the Voriconazole + Caspofungin strategy, which was both costlier and more effective. The associated ICER was 39.899,14 euro per extra life year gained, which is deemed cost-effective when a threshold of 50.000 euro is used. Results were similar to the results in the decision tree of Ament et al. (2007). However, differences with their model include among others higher costs and less life years gained for all strategies and the treatment strategy Voriconazole + Desoxycholate amphotericin B was not dominated by Voriconazole + Caspofungin.

Conclusions: This paper shows that it is possible to build a Markov model for evaluating cost-effectiveness of different treatment strategies for invasive aspergillosis in hematopoietic stem cell transplant recipients, thereby explicitly incorporating the time aspect. Voriconazole + Caspofungin appears to be the preferred treatment strategy based on cost-effectiveness, although evidence is low due to the imperfect data used.

Table of contents

Abstract 2

Introduction 4

Theory 6

- Medical background 6
- Antifungal treatment 7
- Economic evaluation 8
- Decision-analytic modelling 8

Methods 10

- Study population 10
- Cycle length 10
- Time horizon 10
- Perspective 10
- Markov states 11
- Treatment strategies 11
- Transitions 12
- Survival analysis 13
- Costs 14
- Outcomes 14
- Sensitivity analysis 14

Results 16

- Building the model 16
- Outcomes model 24
- Probabilistic sensitivity analysis 27

Discussion 31

- Problems with building the model 31
- Comparison of results with literature 32
- Scientific relevance 33
- Societal relevance 34
- Suggestions for further research 34

Conclusions 36

References 37

Introduction

Patients with a compromised immune system are at serious risk for developing invasive aspergillosis. One important reason why patients are immunocompromised is the receival of a hematopoietic stem cell transplantation. The one-year incidence of invasive aspergillosis among hematopoietic stem cell transplant recipients is between 1,6 and 3% (Kauffman & Gregg, 2015). Overall, there is a probability of 5-13% for stem cell patients to develop invasive aspergillosis (Harman, 2016). Invasive aspergillosis is a systemic fungus infection of the genus aspergillus. Patients with invasive aspergillosis can present themselves with a variety of symptoms, including fever, chest pain, cough, shortness of breath and coughing up of blood (hemoptysis) (Marr, 2015). The prognosis of patients with invasive aspergillosis is poor, due to the aspergillosis itself, but also because of the underlying illness. One-year survival among hematopoietic stem cell transplant recipients with invasive aspergillosis is around 25% (Kontoyiannis et al., 2010).

When bone marrow transplant patients have proven invasive aspergillosis or a high probability of having it, they are treated with antifungal drugs. There are three classes of antifungal drugs that are licensed for treating these patients, which are triazoles (e.g. Voriconazole, Posaconazole), polyenes (e.g. (lipid formulations of) Amphotericin B) and echinocandins (e.g. Caspofungin). The triazoles and the polyenes are approved for first-line treatment, while Caspofungin is not. However, Caspofungin can be used as second-line treatment and in combination with either Amphotericin B or Voriconazole in either first or second-line treatment (Marr, 2017). The guidelines argue that for most patients triazoles should be the cornerstone of the treatment, with echinocandins and polyenes as complementary treatment or as an alternative in case of side-effects, non-response or triazole resistance (Patterson et al., 2016).

Because of the availability of different drugs and the possibility to combine them and switch between them, clinical studies and economic evaluations regarding the best treatment strategy are necessary. Clinical studies of the likes of Herbrecht et al. (2002) and Marr et al. (2004) still have a large influence on guidelines and treatment decisions. They argue that Voriconazole as a monotherapy or in combination with Caspofungin gives clinically the best patient outcomes, while it leads to better short-term survival and fewer side effects. However, those clinical studies only take effects into account, while disregarding costs. For decision making in a broader perspective, costs need to be included, which is done in economic evaluations. The most influential economic evaluations on this subject are the studies of Jansen et al. (2005) and Ament et al. (2007). They conclude that respectively Voriconazole and Voriconazole with Caspofungin are the most cost-effective strategies. Both studies were modeling studies using a decision tree.

Modeling using decision trees, however, has one major limitation. Time is not included in the models of both Ament and Jansen, which means that for example switching between drugs is always at a given moment while clinically those decisions are made on a daily basis for invasive aspergillosis. The time aspect is specifically important in invasive aspergillosis, due to the concavity of the survival curve and the aspect of different dosages of medication over the course of treatment (Herbrecht et al., 2002). Models in which time can be included will therefore better reflect clinical decision making. In contrast to decision trees, a modelling method able to include time is the Markov model. This research will use such a model to study whether accounting for time will change the cost-effectiveness of the possible strategies in treating invasive aspergillosis.

This study will be relevant for decision makers on health care budgets, as it will reveal which strategy for treating invasive aspergillosis in hematopoietic stem cell transplant recipients is best in terms of cost-effectiveness. This information is complementary to that of clinical studies. Moreover, this study

is relevant in a broader scientific point of view, while it will discuss the feasibility of using a Markov model in a patient population suffering from an acute infection. To date, Markov models are mainly used for modeling chronic diseases. Therefore, it will be interesting to see whether Markov modelling offers additional insights on top of the traditional decision tree. This study can be an example for other modeling studies on acute (fungal) infections by elaborating on the advantages and disadvantages of using a Markov model on patients with invasive aspergillosis.

The aim of this research is to assess the cost-effectiveness of the different strategies in treating hematopoietic stem cell transplant recipients with invasive aspergillosis, explicitly considering that patients can switch at any time between health states. Moreover, by relaxing the fixed time definition imposed by decision trees and instead using a Markov model, there will be a second objective of the research. While it is still uncommon to use a Markov model in economic evaluations of acute infections, the objective of the research is also to evaluate the feasibility of using a Markov model in modeling on invasive aspergillosis. This leads to the following research questions, which will be answered in this research:

- Based on cost-effectiveness, what is the preferred strategy in treating invasive aspergillosis in hematopoietic stem cell transplant recipients, considering that patients can switch at any time between health states?
- What is the feasibility and additional value of using a Markov model (and thereby explicitly incorporating the time aspect) in economic evaluations on invasive aspergillosis in comparison with the fixed time definition imposed by decision trees?

The next section will elaborate on the underlying theory used in this study. This section starts with a medical description of invasive aspergillosis in which the epidemiology, pathophysiology and symptoms of invasive aspergillosis will be discussed. Next, there will be a discussion of the most recent clinical research on pharmacological treatment of invasive aspergillosis. In the next sub section, the rationale behind economic evaluation will be described, which will be followed by an explanation of decision-analytic modelling and a discussion why modelling is used in this particular case. The third section will be the methods section. In this section the model will be described along with the general study design. Moreover, decisions regarding the collection of data will be explained together with a discussion on the reliability and validity of this study. Finally, this section will discuss the sensitivity analyses which are performed in the Markov model. The fourth section is the results section. Here, the main results as incremental cost-effectiveness ratio's (ICERs) and net monetary benefits will be presented (NMBs). Moreover, the robustness of those results will be assessed by using the results of the sensitivity analyses. In the discussion, the results presented in the previous section will be put in a broader scientific and societal context. Implications and recommendations based on those results will be formulated. Moreover, the strengths and weaknesses and suggestions for further research will be presented. This paper will end with the conclusions section, in which there will be a concise discussion on the research questions.

Theory

This section provides the theoretical background that is necessary to understand the clinical and scientific relevance of the abovementioned research questions. The first sub section will provide information about the epidemiology, diagnosis and treatment of invasive aspergillosis according to the most recent guidelines. Next, there will be a description of the different pharmacological options to treat invasive aspergillosis, namely amphotericin B, triazoles and echinocandins. The next sub section argues what the relevance of economic evaluations is in the context of health care decision making. The final sub section will bring up arguments about the advantages of modelling in economic evaluations and discusses the differences between on the one hand decision trees and on the other hand Markov models. This will mainly focus on how both models incorporate time.

Medical background

Invasive aspergillosis is caused by an infection of the mold species Aspergillus. Everywhere in the world, people inhale Aspergillus spores every day, but only a small proportion will eventually get ill from it (Paulussen et al., 2017). Aspergillus is a so-called opportunistic pathogen, which implies that healthy people will not suffer from it. However, patients with compromised immune systems can develop some form of aspergillosis (Barnes & Marr, 2006). This can be a relatively mild form like allergic bronchopulmonary aspergillosis (inflammation in the lungs) or aspergilloma (a “fungus ball” usually in the lungs), which have a good prognosis. However, immunocompromised patients can also develop invasive aspergillosis, which is a severe infection in which the aspergillus spores invade the bloodstream and can thereby infect major organs, most frequently the lungs (Denning, 1998). The prognosis of invasive aspergillosis is rather poor with one-year survival between 25% and 59% depending on the underlying disease (Kontoyiannis et al, 2010).

As mentioned above only patients with a compromised immune system are at risk for developing invasive aspergillosis. There are several reasons why people can be immunocompromised. Examples are (leukemia) patients receiving chemotherapy, solid organ transplant recipients and hematopoietic stem cell transplant recipients. The majority of patients who actually develop invasive aspergillosis are hematopoietic stem cell transplant recipients. Three percent of this patient group eventually develops invasive aspergillosis (Carvalho-Dias et al., 2008). A study in France showed that overall there are 1,41 cases of invasive aspergillosis per 100.000 persons per year. While the number of immunocompromised patients is rising worldwide (because of more patients being treated with chemotherapy and the increase in transplantations), invasive aspergillosis is increasingly becoming a health care problem (Bitar et al., 2014).

Symptoms of invasive aspergillus largely depend on which organs are infected. Moreover, patients with invasive aspergillosis have a serious underlying condition, which makes it difficult to distinguish symptoms as belonging to invasive aspergillosis or simply being a consequence of the underlying illness (Barnes & Marr, 2006). Furthermore, symptoms of invasive aspergillosis are rather aspecific and include fever, chest pain, cough, shortness of breath and coughing up of blood (hemoptysis). Taken all together diagnosis based on symptoms alone is very difficult and therefore diagnostic tests are often necessary. The cornerstone of diagnostic tests is taking a culture (which include taking some infected tissue and grow the aspergillus mold outside of the body). However, even after negative diagnostic tests, there is still a probability of invasive aspergillosis (Kauffman et al., 2017).

The abovementioned implies that it is not always clear whether an immunocompromised patient has invasive aspergillosis. This is why the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) has developed a standard set of definitions for invasive aspergillosis (De Pauw et al., 2008). This report states that

immunocompromised patients can have “proven”, “probable” or “possible” invasive aspergillosis. Invasive aspergillosis is proven when a culture shows the aspergillus species. Invasive aspergillosis is probable when a host factor (e.g. hematopoietic stem cell transplantation), clinical features (e.g. radiological findings supporting the diagnosis), and mycological evidence (other than culture) are present. Finally, invasive aspergillosis is possible when a host factor and clinical features are present without mycological evidence (De Pauw et al., 2008).

Whether invasive aspergillosis is proven, probable or possible, influences the treatment strategy. However, much research has also been devoted to whether hematopoietic stem cell transplant recipients should receive prophylactic antifungal therapy. Results of those studies are mixed and it is doubtful whether the benefits of the therapy outweigh the disadvantages (e.g. adverse effects, resistance and high costs) (Wingard et al., 2018). For possible invasive aspergillosis monotherapy with an azole is recommended in the guidelines (Kauffman et al., 2018). Probable and proven aspergillosis are both being treated with an azole and an echinocandin (Kauffman et al., 2018). The remainder of this study will be about the treatment of proven and probable aspergillosis. Although the cornerstone of the treatment is antifungal medication (which will be described in the next sub section), for patients with severe illness, medication alone might not be sufficient. Sometimes surgical removal of a fungus ball can be necessary in selected patients (Patterson et al., 2016).

Antifungal treatment

Over the years, several antifungal agents have been registered for treating invasive aspergillosis (either proven, probable and possible). The first drug that was available was Amphotericin B, which is a polyene. Due to its poor oral absorption, it is mainly given intravenously. One main disadvantage is that a relatively large (80%) proportion of patients receiving Amphotericin B develops renal function impairment (Fanos & Cataldi, 2000). Currently, to avoid nephrotoxicity, lipid formulations of Amphotericin B are preferred to Amphotericin B itself. However, even then there are several side effects related to the use of lipid formulations of Amphotericin B, including infusion reactions, hypokalemia and hypomagnesemia (Patterson et al., 2016). Moreover, clinical outcomes have been relatively poor.

In the early 2000’s, triazoles entered the market and were registered for treating invasive aspergillosis. Because triazoles are mainly metabolized in the liver, nephrotoxicity is not a side effect for this class of drugs. The first triazole on the market was Voriconazole, which can be administered orally and intravenously. In a very influential paper of Herbrecht et al. (2002) clinical superiority of Voriconazole to lipid formulations of Amphotericin B was shown. Moreover, less side effects were noted in the Voriconazole group. Since then, Voriconazole has been recommended to be the first-line treatment in patients with invasive aspergillosis. More recently, other triazoles have entered the market. Most notably are Posaconazole and Isavuconazole. Especially the latter has shown to be noninferior to Voriconazole with less side effects and could therefore be a reasonable alternative (Maertens et al., 2016). Moreover, triazole resistance is increasingly becoming an issue in patients with invasive aspergillosis (Van der Linden et al., 2015). However, drug resistance will not be discussed in this paper.

The third treatment option is the use of echinocandins, including Caspofungin, Micafungin and anidulafungin. The main advantage of this drug class is that there are very little side effects. However, efficacy as a mono therapy is also limited (Cadena et al., 2016). Therefore, it is not recommended to use an echinocandin as first-line treatment. However, it does have a role as salvage therapy once first-line treatment has failed. Recently, there is some research to whether it might be effective to use echinocandins in combination with triazoles. There is a strong indication that Voriconazole combined with Anidulafungin is more effective then Voriconazole (Marr et al., 2015). However, due to a lack of

power, this was not significant. Therefore, more research will be required to see if this combination therapy is indeed a more effective first-line treatment then voriconazole alone.

Economic evaluation

As can be seen in the previous sub section, quite extensive research has been done to the clinical effects of all the available treatment options. While this research is essential for clinical decision making, it is not sufficient for health care decision making (Drummond, 2015). This is where economic evaluations come into place. While resources are scarce and money can only be spent once, it is necessary to also take the costs of the different interventions into account. The main purpose of economic evaluations is to explicitly compare different treatment strategies in a systematic and reproducible manner to enable well-balanced choices about allocating scarce resources to a specific intervention (Drummond, 2015). Choices have to be made in health care and therefore it is better to quantify them.

There are several types of economic evaluations, which include cost-minimization studies, cost- benefit studies, cost-utility studies and cost-effectiveness studies (Drummond, 2015). The latter approach will be used in this paper as will be explained now. In a cost-effectiveness analysis, treatments are compared with regard to the respective costs as well as the effects of the different treatments. The measure of effect can be, for example, costs per life-year gained, which is also the measure of effect used in this study. Since there is no adequate utility measure for patients with invasive aspergillosis, a cost-utility analysis is not feasible. A cost-effectiveness study is particularly useful when two or more alternative treatments have to be compared by, for example, a physician or insurer (Cellini & Kee, 2010). However, in a broader, societal perspective, this method is usually not sufficient, while the outcomes from cost-effectiveness studies are not generalizable to other decisions in or outside of health care. Cost-utility or cost-benefit analyses are better suited in those situations (Drummond, 2015). In this research, we are only interested in comparing different treatment strategies for one illness, namely invasive aspergillosis. Therefore, it is not necessary to perform a cost-utility or cost-benefit analysis. Moreover, the results of this study will be compared with the results of Ament et al. (2007), in which a cost-effectiveness analysis was used. By also using a cost-effectiveness analysis, results will be better comparable.

Decision-analytic modelling

An economic evaluation can sometimes be performed alongside a clinical study. Another possibility, however, is to use decision-analytic modelling. By using a decision-analytic model it is possible to accumulate data from various sources (e.g. trials, expert opinions) (Briggs et al., 2006). This allows comparisons to be made between treatments even though there is not one single trial with all the necessary information. For invasive aspergillosis, there is not one such trial with all necessary data. Mostly, data on costs is not collected in clinical studies. Therefore, in this particular case a model has to be used to bring together all available data. Another advantage of decision-analytic modeling is that all relevant alternatives can be compared in one model even when clinical studies only compare subsets of those (Briggs et al., 2006). This also holds for invasive aspergillosis, while for example the study of Herbrecht et al. (2002) only compares two strategies. Moreover, you can extrapolate over time and while there is no study with a lifetime perspective on invasive aspergillosis (Briggs et al., 2006), this must be done as well. All the above-mentioned points can also be overcome by performing an economic evaluation alongside a new clinical trial. However, this will take longer, will be more expensive and will put patients at risk. Overall, decision-analytic modelling should be used in this study.

Most decision-analytic modelling studies of acute infections use a decision tree. This also holds for economic evaluations of invasive aspergillosis, and as such the most influential studies on this topic use decision trees (Jansen et al. 2005) and (Ament et al. 2007). However, as mentioned in the introduction, this comes with the limitation that time is static in decision trees. Switches (between medication or health states) have to be at a particular moment, which (over)simplifies how switches are really made (Briggs et al., 2006). In the study of Ament for example, when patients switch from first to second-line treatment, they all switch after 5 days. However, in reality patients can switch at any moment of time. Therefore, switching or transition probabilities are represented by non-linear (survival) functions, which cannot be modeled in a decision tree. The time aspect is therefore not considered in the studies of Ament and Jansen.

Time can, however, be included using another decision-analytic model, namely a Markov model (Siebert et al., 2012). In Markov models, "patients" can switch between a limited number of health states. The chance that a patient switches between particular health states is given by transition probabilities, which themselves can be constant or change over time (Briggs et al., 2006). For example, for the latter situation, mortality will likely be higher in the first days of invasive aspergillosis then after several months. This can be reflected in the transition probabilities. Moreover, values for the different states (e.g. costs) can be changed over time. For example, the first days of treatment with voriconazole is usually intravenous, while after due time, this can be switched to voriconazole orally (Herbrecht et al., 2002). The costs of oral and intravenous voriconazole treatment will be different and this can be incorporated in a Markov model.

There are two possibilities of how a Markov model can be performed, namely via cohort simulation or individual (Monte Carlo) simulation (Briggs & Sculpher, 1998). In cohort simulation it is assumed that a hypothetical study population (for example 1000 patients) enter the model in a particular health state and in each cycle some of the patients switch to a different health state. The sum of patients stays the same in each cycle. In individual simulation each patient follows its own path and can be followed through each cycle. The path of each patient is simulated separately. Consequently, variance around the results (e.g. costs, life years gained) can be estimated (Briggs & Sculpher, 1998). However, differences in results between the two models are often negligible (Briggs & Sculpher, 1998). Therefore, the most commonly used approach in modelling literature is the cohort simulation, since it is less complex to execute (Briggs et al., 2006). The cohort simulation will be used in this paper as well.

Mostly, Markov models are used in economic evaluations of chronic diseases, for example in modelling COPD (Menn et al., 2012). However, there are some studies in which a Markov model is used for acute diseases. One such study, which could be relevant as an example for this research, is the one by Manns et al. (2002). Here, they use a Markov model for modelling strategies in treating patients with a severe sepsis. They use the following health states: patient at ICU, patient at ward, patient at home and (the absorbing health state) death. A severe sepsis is, like invasive aspergillosis, an acute disease with a high mortality rate (Gaieski et al., 2013). In the model of Manns, transition probabilities are time dependent and derived from hazard rates. Costs also vary per time period in each health state. Therefore, this model is similar to the approach that will be used here. However, little is described in their study about how they have actually built their model.

Methods

The previous section provided the theoretical background of this study and showed what the additive value of a Markov value is with regard to time compared with a decision tree. In this section, the foundation of the model will be described and choices will be motivated based on recommendations of the ISPOR-SMDM Modeling Good Research Practices Task Force (Siebert et al., 2012). Decisions regarding the study population, cycle length, time horizon, perspective, Markov states, treatment strategies, transitions, survival analysis, costs, outcomes and sensitivity analyses will be discussed here. The model and statistical analyses in this study have been conducted with the use of a combination of Microsoft Excel and Stata.

As mentioned in the introduction, one of the research objectives is to evaluate the feasibility of using a Markov model in an economic evaluation on an acute disease like invasive aspergillosis. While there is little experience of using Markov models in similar acute diseases, there are (to my knowledge) no previous models on which this particular model can be build. Therefore, this model has been developed from scratch and some problems emerged in the process. Since the development of the model is part of the research aims, possible solutions for those particular problems will be given in the results section.

Study population

The study population is defined as adult hematopoietic stem cell transplant recipients with proven or probable invasive aspergillosis. This is motivated by the fact that immunocompromised patients following hematopoietic stem cell transplantation form the largest group of patients with invasive aspergillosis (Morgan et al., 2005). Moreover, it is the same study population as used in Ament et al. (2007). This makes it possible to use part of the data they used and to compare outcomes.

Cycle length

According to Drummond (2015), an appropriate cycle length is one in which a patient will have a low probability of having more than one transition to another state per cycle. Invasive aspergillosis is an acute disease in which switching between states happens daily. In invasive aspergillosis, choices about the (dis)continuation and switching of treatment as well as decisions about discharge from hospital are made on a daily basis. A cycle length of 24 hours is therefore necessary.

Time horizon

Most clinical studies on invasive aspergillosis argue that duration of therapy is at most 12 weeks (Herbrecht et al., 2002). Data about transitions between states is therefore mostly limited to this time frame. Therefore, most cost-effectiveness studies (e.g. the ones by Ament and Jansen) use this time frame in their analysis. However, one advantage of the Markov model is that data can be extrapolated beyond the time for which data is available (Latimer, 2013). This method is already extensively used in research on more chronic conditions (Hwang et al., 1999). By doing this, the time horizon for this study will be extended to 5 years. This time horizon is selected as after 5 years, mortality is approximately 95% in the different models and no patients will receive any kind of treatment for invasive aspergillosis anymore. Further increasing of the time horizon will not change the outcomes while it does add complexity in the model. The results section will discuss parametric extrapolation and the different models used in more depth.

Perspective

The perspective will be the one of the health care purchaser, which in The Netherlands is the perspective of the health care insurer. This means that only health care costs are considered and not broader societal costs such as loss of production. This narrower perspective has been chosen to make

the study comparable with the one performed by Ament et al. (2007) since they use this perspective as well. Moreover, they claim in their article that this perspective is sufficient, as the hospital costs are the majority of costs.

Markov states

The states in a Markov model should be mutually exclusive and collectively exhaustive (Siebert et al., 2012). This means that a patient should always belong to one of the states and not to more than one state at a given time. The Markov states for this model on invasive aspergillosis are:

- First-line treatment
- Second-line treatment
- Other licensed antifungal treatment (OLAT)
- Finished antifungal treatment
- Death (absorbing state)

Those states fulfill both criteria of being mutually exclusive and collectively exhaustive. Moreover, for calculating transition probabilities in this model, only information about, treatment and mortality rates are necessary. However, a model with those states should still give an adequate view of the clinical process of patients with invasive aspergillosis. Given the definition of the patient population no treatment is not included as a Markov state. The respective Markov trace is given in figure 1.

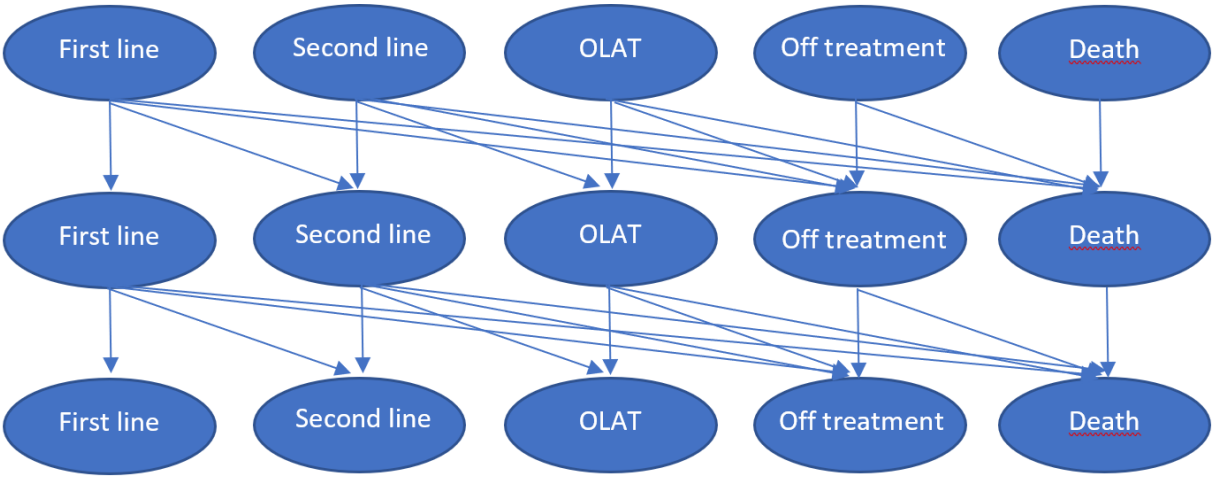

Figure 1: Markov trace

Treatment strategies

Several treatment strategies will now be compared. Those strategies consist of a first-line treatment and a second-line treatment. The same strategies as the ones used by Ament et al. will be used for two reasons. The first reason is that, since their study, guidelines about treating patients have not been changed (Patterson et al., 2016). Moreover, by using the same strategies, outcomes of both studies can be compared, which is one the research goals. Due to a lack of data, two treatment strategies could not be included in the Markov model. Not included is the treatment strategy Voriconazole followed by Liposomal amphotericin B together with Caspofungin and the treatment strategy Liposomal amphotericin B followed by Voriconazole together with Caspofungin. Combination therapies as first-line treatment will also not be included. This is beyond the scope of the current research, due to a lack of data. The treatment strategies are given in table 1. For each strategy, it holds that when both first-line and second-line treatment fail, patients will switch to another licensed antifungal treatment (OLAT), which consists of medicines that have not been used in first- or second-

line treatment. The choice of OLAT can differ even within treatment strategies based on the clinical decision of the physician.

First-line treatment	Second-line treatment
Voriconazole	Liposomal amphotericin B
Voriconazole	Caspofungin
Voriconazole	Desoxycholate amphotericin B
Liposomal amphotericin B	Voriconazole
Liposomal amphotericin B	Caspofungin

Table 1: Treatment strategies

Transitions

Figure 1 already showed the five health states that are used in the Markov model with the possible transitions between the health states. This is the basis of the Markov traces for the respective treatment strategies. There are two different ways to actually fill in those Markov traces. The first option is to assign probabilities to all different transitions from one health state to another. However, it would be very difficult to obtain data about all the possible transitions in all 5 health states at every point in time for each treatment strategy. For an extensive model, such as this one, this is not feasible. The second option is to use 'survival' curves for each health state. This would mean that only individual patient data regarding survival and which treatment a patient is on over time, would be necessary to build Markov traces. Therefore, this is the approach that will be used in this paper. It will be explained how the Markov traces were eventually obtained. In this section, there will be an explanation on how 'individual patient data' was created based on the study of Ament, since real individual patient data was unavailable. In the results section, there will be a discussion on how parametric extrapolation of the data has been applied and which advantages and disadvantages are associated with different possible distributions. Furthermore, the results section will describe the distribution that was eventually used to come to the appropriate Markov traces.

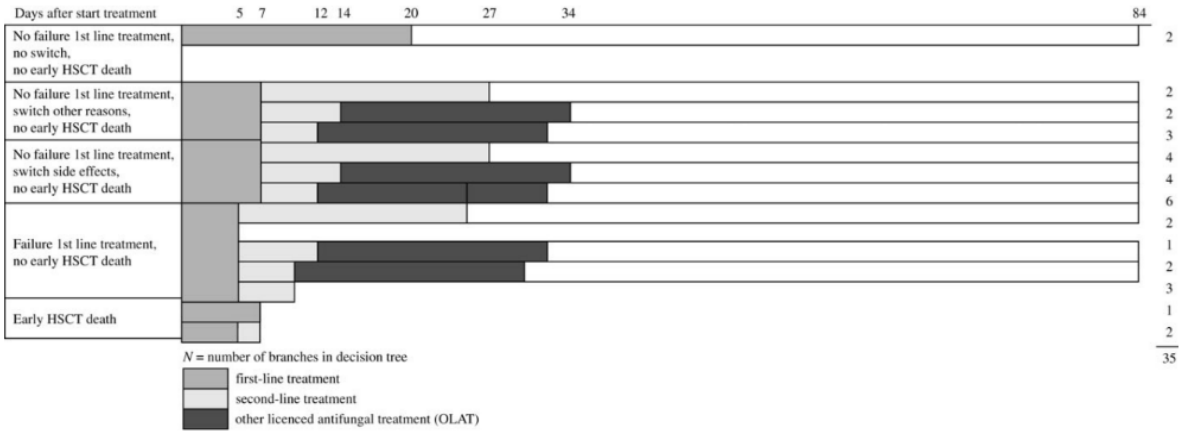

Figure 2: Time points when patients switch in the study of Ament et al. (2007)

Individual patient data is necessary to be able to estimate survival curves and consequently Markov traces. Unfortunately, no individual patient data was available for this patient population. Therefore, patient data on the level of the individual patient had to be developed based on the data used by the paper of Ament et al. (2007). Figure 2 shows that in their research, there were also some time points included in which patients could switch from treatment or when patients could die. Based on this data and the transition probabilities for the different drugs used in their paper, it is possible to derive Kaplan Meier curves and thereby patient data on the level of the individual patient. Kaplan Meier curves were estimated for the following situations:

- Overall survival
- On any antifungal treatment
- On first- or second-line treatment
- On first-line treatment

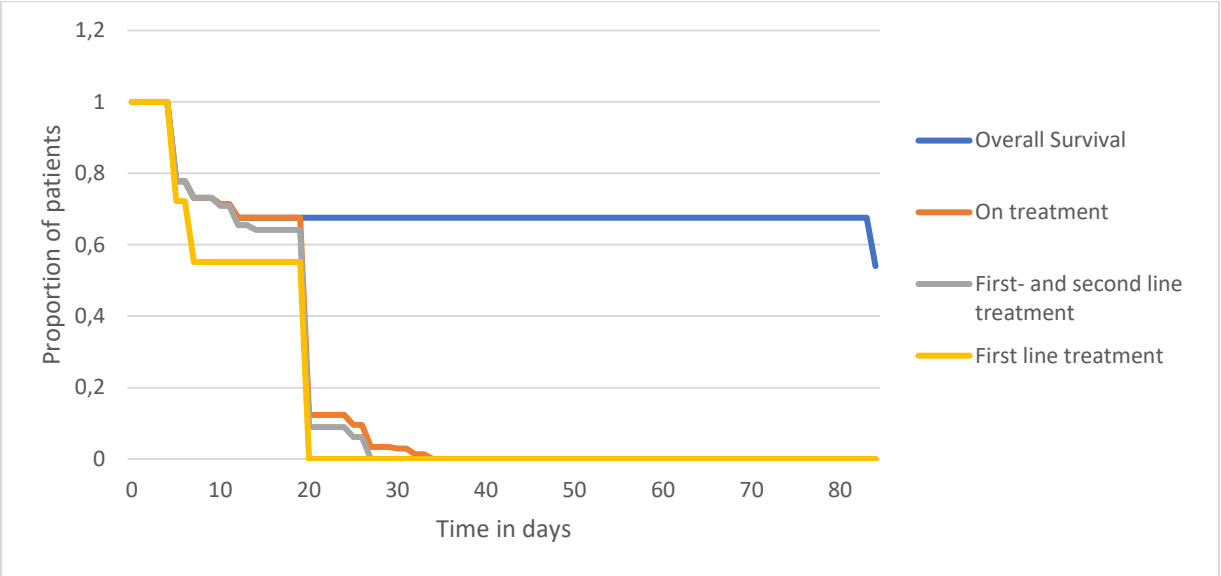

Figure 3: Kaplan Meier Voriconazole + Liposomal amphotericin B

Figure 3 shows the Kaplan Meier curves for the Voriconazole and Liposomal amphotericin B treatment strategy. It can be seen that there are only limited time points in which patients can switch. The nature of the data and the small number of observations are obviously not ideal and this means that the results of this study have no significant clinical relevance. Nevertheless, this will provide a blueprint for studies when appropriate individual patient data is available.

Having the Kaplan Meier curves as presented in figure 3 is not sufficient for the Markov traces. The next step is to derive the patient data on an individual patient level for this. This has been done by creating a virtual patient group of 1000 patients who switch at the given times by the Kaplan Meier curves (such as those given in figure 3). At this point, by using survival analysis, the created data can be parametrically extrapolated using various distributions to derive Markov traces that can be implemented in the model.

Survival analysis

The Kaplan Meier curves as presented in figure 3 could be used for the Markov traces, but doing this has some important disadvantages. The first problem is that there are only limited points of time in which patients can switch from one health state to another, while in real life treatments are switched on a daily basis and deceasing can happen on any moment. To account for this, data must be fitted through the observations to get a smooth line, which realistically covers the actual transition probabilities. Furthermore, the Kaplan Meier curves only give information for up to 12 weeks after starting treatment. And for our model to have a time horizon of 5 years, data needs to be extrapolated beyond those 12 weeks.

These two problems occur when using non-parametric survival functions like the functions in figure 3. Both problems can be solved by using parametric extrapolation of the survival functions. Different distributions can be used for extrapolating the data and include Weibull, Exponential, Gompertz and Loglogistic. While all those distributions have different properties and thereby different outcomes, all

the previously mentioned distributions have been used for estimating the Markov traces and will be systemically compared in this study based on the guidelines provided by NICE (Latimer, 2013). Criteria that will be used include theoretical considerations, visual inspection, statistical tests, tails of the distribution and negative patient values. Moreover, problems with different distributions will be discussed and possible solutions for these problems are given in the results section.

Costs

Costs included for patients on treatment are treatment costs, costs of adverse events and hospitalization costs. For the baseline model, those costs are derived from Ament et al. (2007), as this makes results comparable. A different scenario will be run in which the most recent costs of the different treatment strategies will be used (see table 2). An important change in prices from 2007 to 2018 is for the treatment costs of Voriconazole, since in 2011 the patent expired. Based on the structure of a Markov model, several assumptions had to be made to enable those costs to be included. These assumptions will be discussed in the results section.

Costs for patient off treatment are costs for hematopoietic stem cell patients based on the paper of Saito (2008), which are only included in the baseline model. These costs include, among others, hospitalization costs, treatment for the underlying disease and treatment for other infections. Those costs are not used in patients on treatment, while that would mean that certain costs overlap, such as hospitalization costs. Therefore, this would lead to an overestimation of costs. Those costs are not used in the paper of Ament et al. (2007), but they are significant and need to be included in the model. Patients who have been successfully treated for their invasive aspergillosis will not be completely healthy, since they are still hematopoietic stem cell transplant recipients and therefore at risk for many other illnesses. Both for comparison of the treatments under consideration as in comparisons in a broader context, it is necessary to include such costs. In the baseline model those costs are excluded for the comparison with the results of Ament.

All costs are in euros and have been adjusted for inflation using the consumer price index (CPI). No half-cycle correction or discounting has been used because of the short time period of the model.

Outcomes

For every strategy, the expected costs and life years gained are calculated. With those measures, it is possible to calculate the main outcome of the study, which is costs per life-year gained. Quality of life has not been incorporated in the model, due to the non-existence of valid quality of life measures for the different health states. Besides, it is unclear whether survivors of invasive aspergillosis have a worse quality of life then hematopoietic stem cell transplant recipients who did not develop invasive aspergillosis. Moreover, previous economic evaluations on invasive aspergillosis also used cost of life-year gained as a measure (Ament et al., 2007; Jansen et al., 2005). By having the same outcome, measure results of these studies and studies using decision trees become comparable, which is one of the research goals. The strategy with the lowest cost is used as the reference category. For more effective treatment strategies, incremental cost-effectiveness ratio's (ICER) and net monetary benefits (NMB) are calculated. Based on the cut-off values used in The Netherlands, a willingness to pay 50.000 euro will be used as a threshold to decide whether a treatment is deemed cost-effective compared to the other (Zwaap et al., 2015).

Sensitivity analysis

As already mentioned, the baseline model will be performed with data from the paper of Ament et al (2007). A second model will be executed with the most up to date information on treatment costs, which has two objectives. First, this model will give information on which treatment strategy is most cost-effective in the current situation, given the current drug prices. Moreover, this second model will

be used to assess the robustness of the model to some extent, namely with regard changes in prices. In that way, it can be seen as a form of a deterministic sensitivity analysis. Table 2 gives an overview of the variables that have been used in both models. Furthermore, a probabilistic sensitivity analysis has been performed.

	Value 2018	Value 2007
Daily costs Voriconazole IV	324,75	429,00
Daily costs Voriconazole orally	8,30	70,60
Daily costs Liposomal amphotericin B	856,62	1225,21
Daily costs Caspofungin	343,34	478,00
Daily costs Desoxycholate amphotericin B	31,24	29,48
Hospital costs	596,32	500,00
Costs adverse events Voriconazole	596,32	500,00
Costs adverse events Liposomal Amphotericin B	1788,95	1500,00
Costs adverse events Caspofungin	0,00	0,00
Costs adverse events Desoxycholate amphotericin B	3577,91	3000,00
Daily costs Hematopoietic stem cell transplantation recipient*	108,95	Not included

Table 2: Costs used in baseline model and 2018 model, 2018 prices are Dutch retail prices in November 2018

* not included in the paper of Ament et al. (2007), retrieved from Saito et al. (2005)

Results

The previous section described the theoretical consideration which forms the basis of the Markov model. However, the process of building the actual model was not straightforward. The problems and challenges in building the model will be discussed in this section. First, several assumptions had to be made for converting costs from the Ament decision tree to our Markov model. Next, the process of retrieving the respective Markov traces will be described. Thereafter, this section will present the results of both the baseline model and the 2018 model. This section ends with a description of the results of the probabilistic sensitivity analysis that has been performed.

Building the model

Assumptions costs

The treatment costs of Liposomal amphotericin B, Desoxycholate amphotericin B and Caspofungin could simply be transferred from the decision tree of Ament to the Markov model. However, Voriconazole has two routes of administration namely orally and intravenously with differing costs. Therefore, a choice must be made which patients receive Voriconazole via which routes. For Voriconazole as a first-line treatment, the first 10 days of treatment will be given intravenously and thereafter the route of administration will be orally. According to the literature, Voriconazole must be given intravenously for at least 7 days (Thompson & Lat, 2001). However, when the clinical condition of patients is too poor, switching to Voriconazole orally can be postponed. The period of 10 days to switch the route of administration for Voriconazole is used in Ament as well. To conclude, the cost of the Markov state “Voriconazole” as a first-line treatment is determined to be equal to the costs of intravenous Voriconazole in the first ten days, while after 10 days it is equal to the costs of oral Voriconazole.

Voriconazole as a second-line treatment is always given intravenously for two reasons. The first reason is that a Markov model does not have a memory, which means that it is not possible to follow individual patients going through the different Markov states. Therefore, it is not possible to implement in the Markov model that patients receiving second-line treatment receive Voriconazole intravenously for some amount of time, before they switch to Voriconazole orally. The second reason is that switching from first to second-line treatment often indicates that the patient is not in an adequate condition to receive voriconazole orally (Perea et al., 2004). Therefore, it is most likely that when Voriconazole is used in the clinical setting, it will be administered intravenously.

The costs of OLAT were calculated as an average of the costs of the treatments which are not used in first- or second-line. This approach is similar to the one used in Ament et al. (2007)

Adverse events costs can only be estimated for the first-line treatment strategy. As already explained above, one of the characteristics of Markov modeling is that there is no history in the model. Another consequence of having no memory in a Markov model is that it is impossible to exactly verify how many of the patients eventually will receive second-line treatment or OLAT, which makes it also impossible to determine how many patients will experience an adverse event during the time period covered by the model. Therefore, it is difficult to get reasonable estimates for the costs of adverse events for second-line treatment and OLAT. Nevertheless, it is important to include costs for adverse events for second-line treatment (and OLAT) in the model. The number of adverse events is based on the maximum number of patients which were on any moment receiving second-line treatment or OLAT, respectively. The costs of adverse events were calculated by multiplying the average costs when side effects occur by the probability that an individual will experience an adverse event from this treatment.

Hospitalization costs are retrieved from the paper of Ament et al. (2007) and used in all patients on treatment (first-line, second-line and OLAT). One advantage of the possibility to administer Voriconazole orally is that it can be used to treat patients out of hospital, which would mean lower hospitalization costs. However, it has been shown that there is no difference in the amount of hospitalization days between treating invasive aspergillosis with Voriconazole or Amphotericin B (Wingard et al., 2007). Based on this finding, hospitalization costs are also included for patients who receive Voriconazole orally.

Comparison of distributions for survival analysis

As mentioned in the methods section, survival analysis will be used to retrieve the respective Markov traces for the model. To achieve this, it is necessary to use parametric extrapolation on the (manually derived) survival data retrieved from Ament et al. (2007). Different distributions can be used for this parametric extrapolation of survival data. Most frequently used are the Weibull, Exponential, Gompertz, Loglogistic and lognormal models. Those models all have different underlying assumptions and choosing one of them can affect outcomes significantly (as is the case in our study, which will be shown in the results section). Moreover, there is no "one size fits all" model, as it depends on the underlying characteristics of the study population which distribution can accurately represent that same study population. Therefore, it is important to systematically assess which distribution should be used in an economic evaluation. This paper will use the algorithm provide by NICE to evaluate which distribution is most appropriate to use (Latimer, 2013). The above-mentioned models will be compared based on underlying theory, visual inspection, negative patient values, tails and the Akaike information criterion (AIC). The lognormal model is not estimated while this model is very much comparable to the loglogistic model with respect to both underlying assumptions and outcomes.

Theory

The exponential distribution has a constant hazard rate and therefore the survivor function is given by: $S(t)=e^{-\lambda t}$. It is only appropriate to use this distribution when the probability that an event occurs is the same over the whole duration of the model. For both the survival function and the treatment functions it is doubtful that the assumption of a constant hazard rate holds. Overall survival studies show that the mortality rate in the first weeks after diagnosis is much higher than in the weeks and months thereafter (Marr et al., 2002). Therefore, it appears that a declining hazard rate will better describe overall survival than a constant hazard rate. Another argument can be given for treatment duration. It is not likely that patients will switch during the first day that they receive treatment, while it takes some time before the effects of that particular therapy are visible. Therefore, the probability of switching between treatments or going off treatment will initially be low and increase over time. However, most treatments have a maximum duration. In invasive aspergillosis, treatment is hardly given longer than 12 weeks (Herbrecht et al., 2002). Therefore, it seems that the treatment curves are initially characterized by an increasing hazard rate followed by a decreasing hazard rate. To conclude, it appears that the exponential distribution is too simplistic to use in our model.

The survivor function of the Weibull distribution is given by: $S(t)=e^{-\lambda t^{\gamma}}$. It has a shape parameter (γ) and a scale parameter (λ), which means that this distribution is not restricted to the assumption of a constant hazard rate. Instead, the Weibull distribution is characterized by monotonic hazards, which means that the hazard rate can only increase (when $\gamma>1$) or decrease (when $\gamma<1$), but not change direction. As mentioned above, this seems suitable for estimating the overall survival curve. However, the treatment curves violate the assumption of monotonic hazards, as the hazard rate first increases and then decreases. The exponential distribution is actually a special case of the Weibull distribution, when $\gamma=1$.

The survivor function of the Gompertz distribution is given by: $S(t)=e^{\frac{\lambda}{\gamma}(1-e^{-\gamma t})}$. Similar to the Weibull distribution, it has a shape parameter (γ) and a scale parameter (λ). However, an important characteristic of the Gompertz distribution is that when the shape parameter is negative, then the survivor function will never decrease to 0. In our model, the survivor function does have a shape parameter lower than 0, which would mean that some patients will never die, which is clearly not possible. A possible solution for this problem is given in the next sub section. Moreover, the assumption of monotonic hazards has to be met as well for the Gompertz model to be valid. As mentioned above, this will likely not be the case in the treatment functions.

The final model is the loglogistic model, which has the following survivor function: $S(t)=(1+e^{\theta}t^{\kappa})^{-1}$. In this model, hazards can be non-monotonic with respect to time, which is the case when κ>1. In that situation the hazard rate will first increase and then decrease, which is expected to be the case for the treatment curves. However, because of its functional form the loglogistic model always has very long tails, which will be discussed further down in this sub section.

Visual inspection

In many economic evaluations, model selection is only based on visual inspection (Latimer, 2013), which is often not sufficient. Because of censoring or having few observations on the original Kaplan Meier curve, visual inspections often become unreliable. However, it is still a good method to visually see which models are clearly not representative for the population in the study. First, the overall survival curve will be observed, which is shown for the Voriconazole + Liposomal amphotericin B treatment strategy in figure 4.

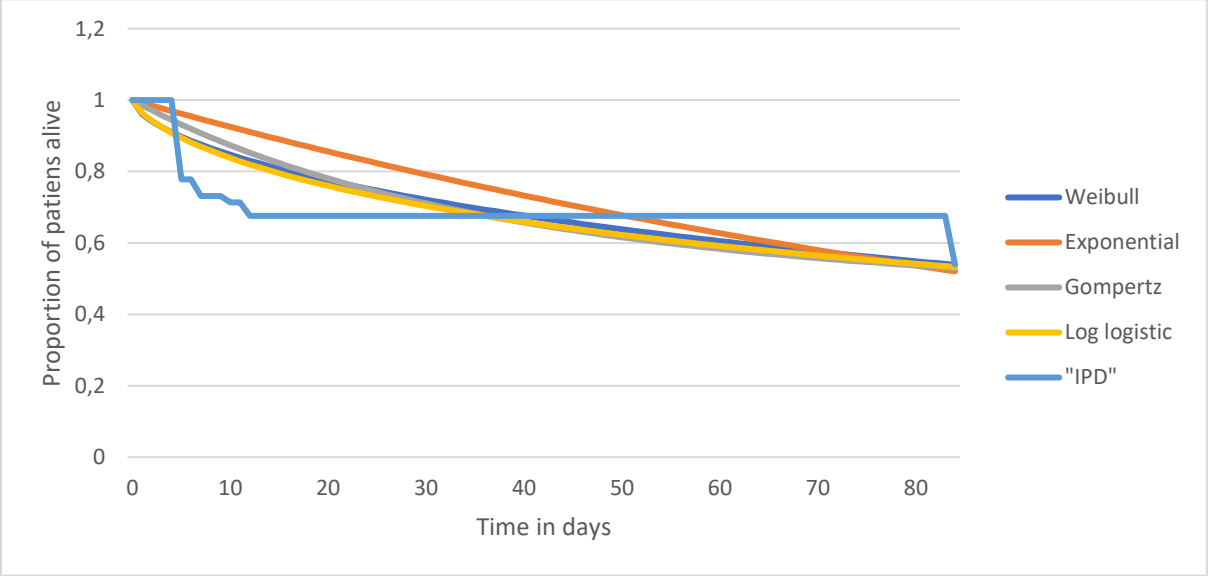

Figure 4: Overall survival curves for different distributions

The time horizon of the figure has been set to 12 weeks, which is the length for which data was available in the paper of Ament. The tails will be discussed separately. It can be seen that after 12 weeks all models have approximately the same overall survival, but the course differs. The main outlier is the exponential model which is less concave than the other models. This is less realistic while this means that there is less difference between mortality in the first weeks and mortality in later weeks. The data of Ament suggests that this is not the case, which is similar to what theory suggested as mentioned above. This supports the claim that survival is not characterized by a constant hazard rate and that therefore the exponential model is not a suitable model for survival in this particular patient population. The other curves are visually similar to each other.

Figure 5 shows the treatment curves (on first or second-line treatment) that are estimated by the different models next to data derived from the study of Ament. It can be seen that the original data is characterized by a sort of plateau in the first weeks followed by a steep drop after 3 weeks, which is most frequently the standard duration of treatment for patients with invasive aspergillosis. The Weibull, Gompertz and loglogistic follow more or less the same pattern. However, there is a difference between the Gompertz curve on the one hand versus the Loglogistic curve on the other. In the Gompertz model, the estimated proportion of patients on treatment drops early to zero, comparable to the original data, while in the loglogistic model this happens more gradually. The Weibull curve lies somewhat in between those two models. Moreover, the clear outlier is again the exponential curve, due to its constant hazard rate. Visually, this model is least fitted to the original Kaplan Meier curve.

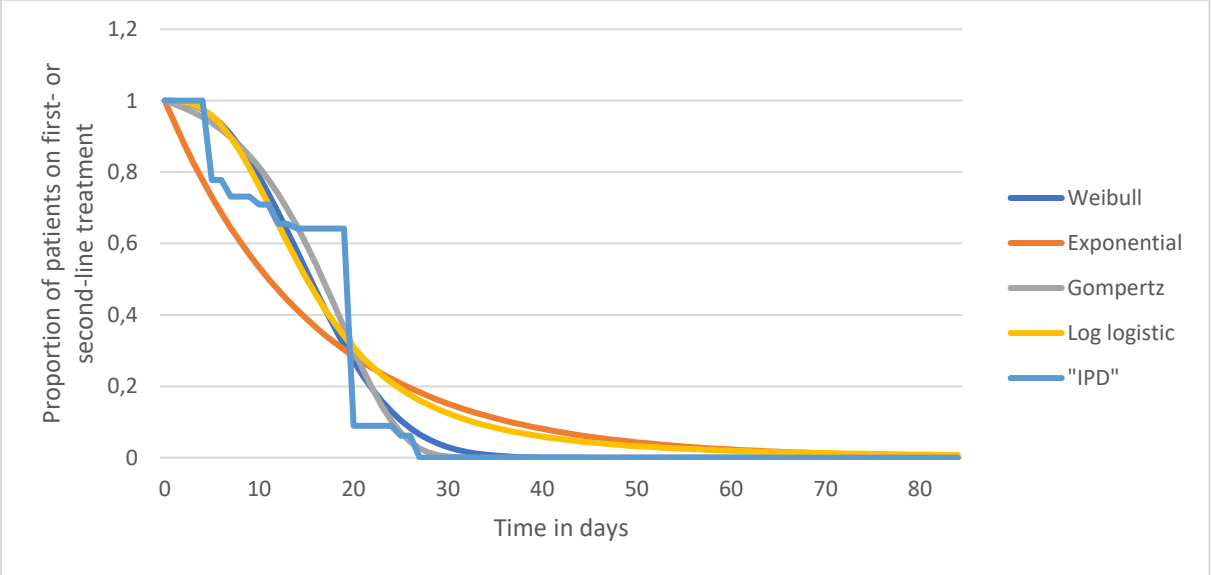

Figure 5: Treatment curves (on first- or second-line treatment) for different distributions

Negative patient values

When running the different models, it appeared that in the Weibull, Gompertz and Loglogistic model there were at some time points negative patient values. Figure 6 gives an example of this problem in the loglogistic model for the Voriconazole + Liposomal amphotericin B treatment strategy. It can be seen that in the first week, there are more patients on treatment than there are patients alive. Obviously, this is not possible and could even bias the results. In the loglogistic model, these effects are the largest, but the problem also occurs in the Weibull and Gompertz model. Only the exponential model does not show negative patient values in its respective Markov trace (Figure 7). This is a consequence of the functional form of its survival function. While the other models all have two parameters of which one is a shape parameter, the exponential model does not have such a shape parameter, which implies that curves fitted with the exponential distribution can never cross each other.

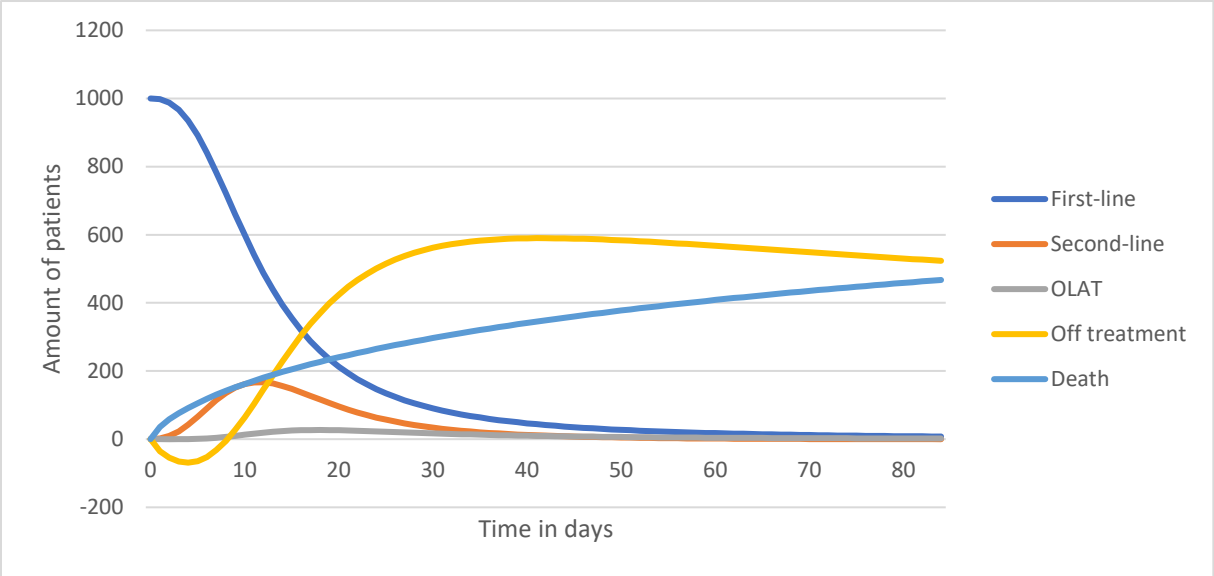

Figure 6: Markov trace of loglogistic model of the Voriconazole + Liposomal amphotericin B strategy

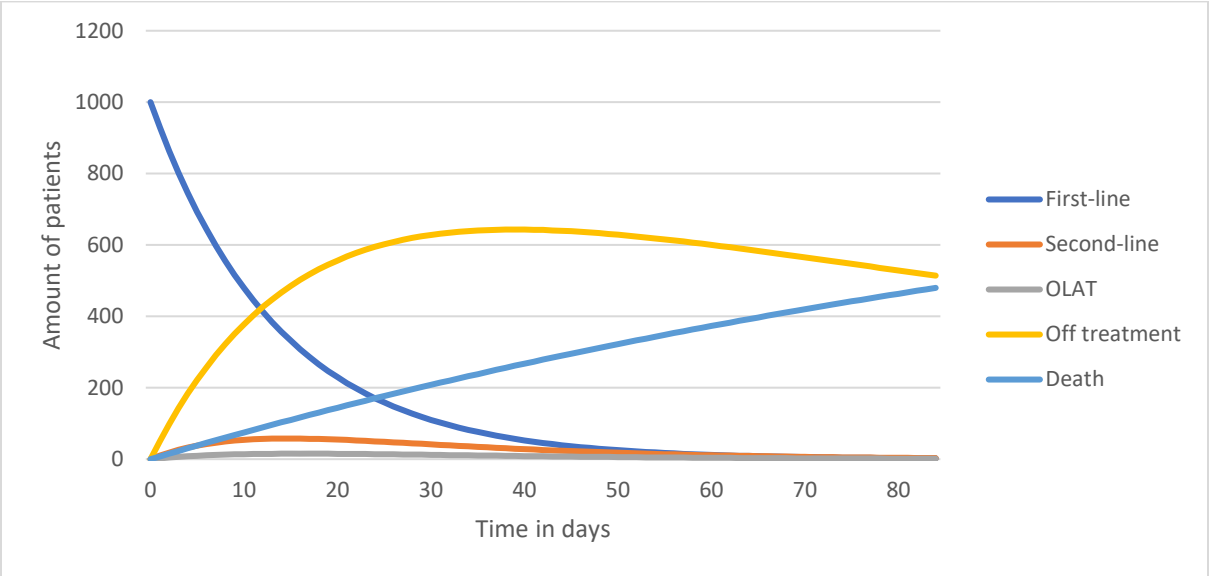

Figure 7: Markov trace of exponential model of the Voriconazole + Liposomal amphotericin B strategy

Tails

One important reason to use parametric extrapolation is to be able to estimate a survival function for a longer time period than for which data is available. While the other criteria used in this sub section give information on the internal validity (how well does the model fit the observed data), the tails provide information on the external validity (is the data realistically estimated beyond the time horizon of the original study) (Collett, 2015). There is no objective statistical test for testing external validity and therefore this can only be checked by looking at the tails of the respective models.

The model with the shortest tails is the Gompertz model. In this model, after approximately eleven weeks in all treatment strategies, all patients are off treatment. Moreover, as explained above, due to the negative shape parameter after one year an equilibrium is reached in which no patients will die anymore. This means external validity in this model is very low regarding overall survival. However, in the next sub section a possible solution to this problem is presented. The other extreme is the

loglogistic model in which there are very long tails, with after 5 years still 10 percent survival and even patients still being on treatment. The exponential and Weibull curves are characterized by tails of intermediate length.

Akaike information criterion

Statistical tests can also help to select the model. The test that is most frequently used is the Akaike information criterion (AIC). The idea behind the AIC is to find the model which minimizes the information that is lost by modeling. The AIC can be used to find the model with the best fit and with a minimum of parameters (Burnham & Anderson, 2010). The Weibull, Gompertz and Loglogistic all have 2 parameters instead of the one parameter used by the exponential model. The suitability is per definition equal or higher when more parameters are used. However, the explanatory power of the model is not necessarily higher when more parameters are used and therefore models with more parameters are penalized by the AIC. Table 3 shows the results of the AIC for the different models in the Voriconazole + Liposomal amphotericin B treatment strategy. The lower the AIC the less information is lost by the model. According to the AIC the Loglogistic model is best in estimating the survival function, while the AIC is lowest in the Gompertz model for estimating the three different treatment curves. However, nothing can be said about the (un)certainty of these results.

	Exponential	Weibull	Gompertz	Loglogistic
Overall survival	302,31	289,02	295,47	287,41
On treatment	233,79	164,92	152,40	198,89
On first- or second-line treatment	231,98	156,94	136,65	193,14
On first-line treatment	238,05	185,89	171,65	211,23

Table 3 Akaike information criterion for the different survival curves for each model

Another test that can be used for comparing the suitability of the models is the log cumulative hazard plot, which is used to evaluate the hazard function. As earlier mentioned, different models assume different hazard rates (e.g. a constant hazard rate is assumed in the exponential model). This can be visualized with a log cumulative hazard plot. However, while there are so little switching points and the fact that no real individual patient data is used, such a hazard plot will not give additional information over the theoretical argumentation on how the hazard rate will behave over time. Therefore, the log cumulative hazard plot has not been used in this study, but when real individual patient data is available, this will be a useful test.

Problems in distributions

The previous sub section showed that some problems occurred in the different models used. The two main problems and possible solutions will be discussed in this sub section. First, we will look at the problem of negative patient amounts in the Weibull, Gompertz and Loglogistic models. There were negative patient values in the off treatment, OLAT and second-line treatment groups and possible solutions will be formulated.

- The group of patients off treatment was negative in the first cycles of the model, which can be seen in figure 6. While this is not possible, in days where there were negative patient amounts, the amount of patients in this health state has been put to zero. However, without other adjustments this would lead to more patients being in the model than theoretically possible. To solve this, the same amount of patients added in the off treatment group had to be deducted from another group. Based on earlier research (see figure 8), it is known that in the first days of treatment mortality is highest (Barnes & Marr, 2007). Therefore, it is not reasonable to deduct those patients from the “death” group. Furthermore, the second-line

treatment and OLAT treatment groups have too few or even negative patient numbers themselves. So, the only reasonable option is to deduct those patients from the first-line treatment group.

- The negative patient values in the OLAT group were also in the beginning of the first days of the model, although to a less extent. Therefore, a similar argument as above holds for the negative amount of patient in the OLAT group. However, while the amount of negative patients is less in this group, it is possible to deduct those patients from the second-line treatment group.
- The negative patient values in the second-line treatment group are in contrast to the negative patient values in the off treatment and OLAT groups in the tail of the distribution. To correct this, those patients are deducted from first-line treatment group. The negative patient numbers in this group in the Weibull distribution are relatively small compared to, in particular, the off treatment group. However, in the loglogistic distribution the problem with the negative patient numbers in the tail of the distribution is larger due to the longer tails associated with the loglogistic distribution.

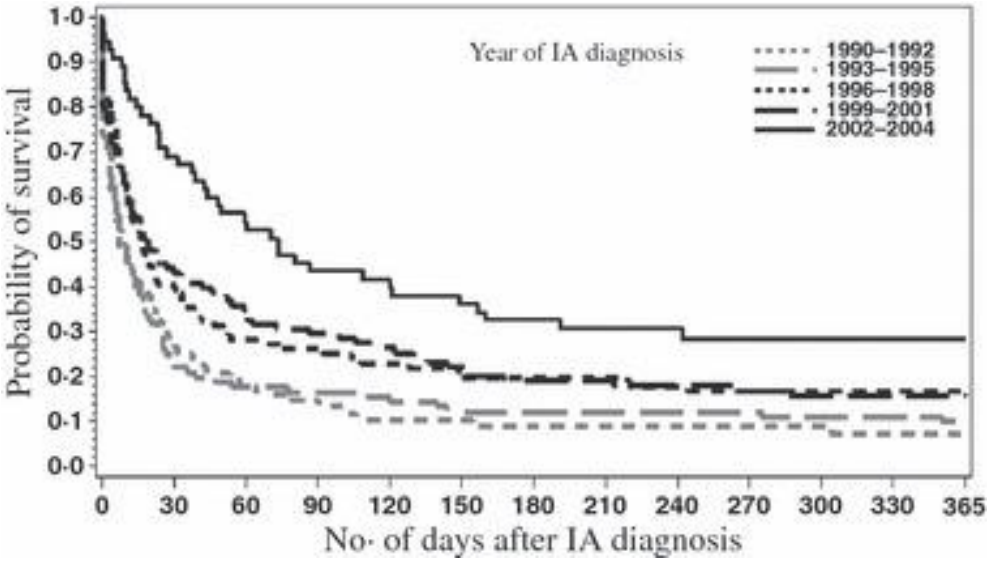

Figure 8: Observed mortality in patients diagnosed with invasive aspergillosis, retrieved from Barnes & Marr (2007)

The other problem as described in the previous sub section is that in the Gompertz distribution overall survival stagnates at 40-50 percent, which is a characteristic of the Gompertz distribution when the gamma is below 0, which is the case in all treatment strategies. Therefore, extrapolating data beyond the period for which there is data (in this case 12 weeks) is not reasonable. So, this time period is used for the Markov model while using the Gompertz distribution. Survivors after 12 weeks are expected to live for 2,3 years longer as this is the mean survival for hematopoietic stem cell transplant recipients (Ament et al., 2007).

The preferred model

This section has shown that there is not a single distribution which is clearly better than either of the others. Moreover, some survival functions seem better suited to estimate the Kaplan Meyer survival curve than to estimate the treatment curves and the other way around. Therefore, in the preferred model, a different distribution will be used to estimate the survival curve than the distribution that will be used for the parametric extrapolation of the treatment curves.

For the estimation of the survival curve, the Weibull distribution will be used. As explained above, for the survival curve, the monotonic hazards assumption seems to hold, which is an important assumption of the Weibull curve. Visually, the Weibull curve seems to fit the original data well and the AIC of the Weibull curve is second lowest, fractionally behind the Loglogistic distribution. However, the loglogistic distribution has a very long tail, which is according to theory not realistic.

For the estimation of the treatment curves, the Gompertz distribution will be used in the preferred model. The Gompertz distribution visually seems to fit the original curve the best, while also clearly having the lowest AIC for all three curves. Moreover, the amount of negative patients is lower than in the Weibull and Loglogistic model. Although, it is doubtful that the monotonic hazard assumption is met in the treatment curves, the Gompertz model does seem to have the best goodness of fit and will be used in the preferred model throughout this study.

Figure 9 shows the Markov trace of the preferred model, with the adjustments performed to avoid negative patient values as discussed in the previous sub section.

Survival curve	Distribution
Overall survival	Weibull
On any antifungal treatment	Gompertz
On first- or second-line treatment	Gompertz
On first-line treatment	Gompertz

Table 4: Distributions used for the different survival curves

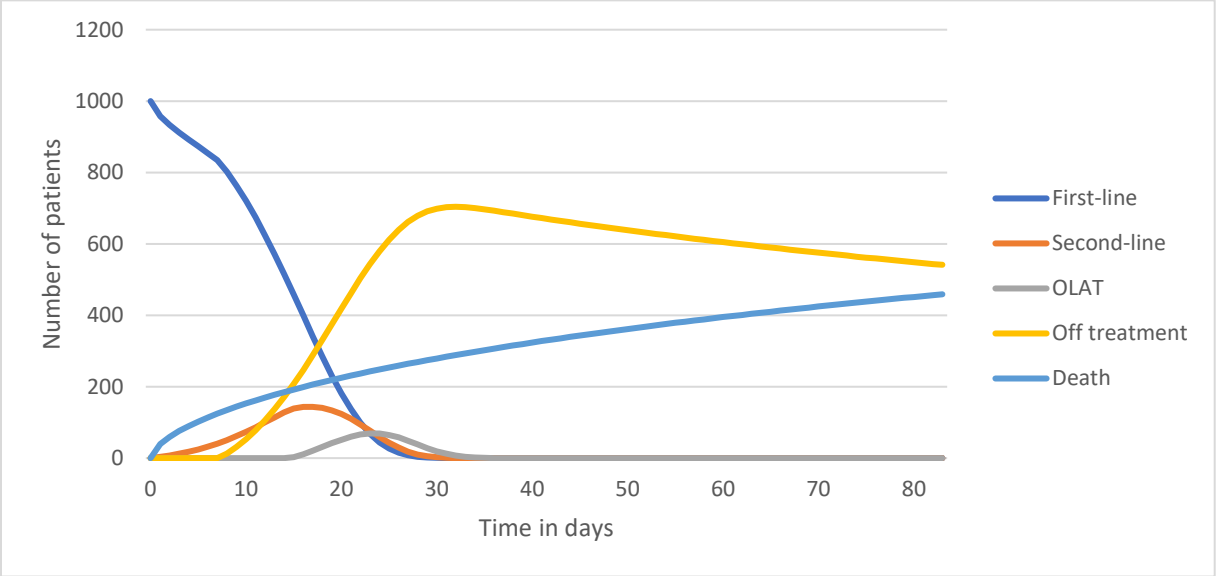

Figure 9: Markov trace of the preferred model of the Voriconazole + Liposomal amphotericin B strategy

Outcomes model

Baseline model

The costs and amount of life years for the different treatment strategies in the baseline model are presented in table 4. As indicated, costs range from 14,137 euro for the Voriconazole + Desoxycholate amphotericin B strategy to 24,956 euro for the Liposomal amphotericin B + Voriconazole strategy. The Liposomal amphotericin B + Caspofungin strategy is the least effective while patients live on average just 0.57 life years longer, while the Voriconazole + Caspofungin strategy appears to be the most effective with 0.73 life years gained. Three strategies are less or equally effective than the cheapest treatment strategy, namely Voriconazole + Liposomal amphotericin B, Liposomal amphotericin B + Voriconazole and Liposomal amphotericin B + Caspofungin. Those strategies are thereby dominated by the Voriconazole + Desoxycholate amphotericin B strategy. However, Voriconazole + Caspofungin is (although more expensive) more effective. The corresponding incremental cost-effectiveness ratio (ICER) is 2108.29 euro for each additional life-year. The net monetary benefit (NMB) has also been calculated. The threshold has been set to 50,000 euro per life year, which is used in the Netherlands (Zwaap et al., 2015). The NMB for Voriconazole + Caspofungin compared with Voriconazole + Desoxycholate amphotericin B is 1633.30 euro. Since the NMB is positive, with this particular threshold, the Voriconazole + Caspofungin strategy is preferred.

Treatment	Costs	Life years	Costs per LY gained	ICER
Voriconazole + liposomal amphotericin B	15,426.37	0.69	22,300.18	Dominated
Voriconazole + caspofungin	14,208.79	0.73	19,575.00	2108.29
Voriconazole + desoxycholate amphotericin B	14,136.89	0.69	20,436.12	
Liposomal amphotericin B + voriconazole	24,955.88	0.60	41,520.98	Dominated
Liposomal amphotericin B + caspofungin	24,935.86	0.57	43,924.59	Dominated

Table 4: Outcomes baseline model

When looking at the ICERs for different models, there are some differences as can be seen in table 5. The preferred model has the lowest ICER, while the exponential model gives an ICER for Voriconazole + Caspofungin compared to Voriconazole + Desoxycholate amphotericin B of 22,766.41 euro. Although the ICERs are quite different along the models, the costs and effects rank the same among the models. This means that the Voriconazole + Liposomal amphotericin B, Liposomal amphotericin B + Voriconazole and Liposomal amphotericin B + Caspofungin are dominated regardless which model is used.

Model	ICER Voriconazole + caspofungin vs Voriconazole + desoxycholate amphotericin B
Weibull	€ 3969.79
Exponential	€ 22,766.41
Gompertz	€ 4557.24
Loglogistic	€ 7311.84
Preferred	€ 2108.29

Table 5: Differences in ICERs in the baseline model

2018 model

When the model is run with cost information from 2018, results are different in some respects. Costs are higher for all treatment strategies varying from 39,838 euro for Voriconazole + Desoxycholate amphotericin B to 43,667 euro for Liposomal amphotericin B + Voriconazole as illustrated in table 6. Effects are obviously the same as in the baseline model, as the Markov traces have not been changed. The same treatment strategies are dominated in the 2018 model as well. The only ICER that has to be calculated, is the one for Voriconazole + Caspofungin compared with Voriconazole + Desoxycholate amphotericin B. The respective ICER is 39,899.14 euro. The difference in ICER between the models is smaller as can be seen in table 7. The NMB for Voriconazole + Caspofungin compared with Voriconazole + Desoxycholate amphotericin B is 344.48 euro. While the NMB is positive, with the limit of 50,000 euro per life year gained, the Voriconazole + Caspofungin strategy is preferred. However, this is dependent on which distribution is used, while with the exponential distribution, the NMB is -37.76 euro, which means that the Voriconazole + Desoxycholate amphotericin B would be the preferred strategy.

Treatment	Costs	Life years	Costs per LY gained
Voriconazole + liposomal amphotericin B	40,671.81	0.69	58,794.67
Voriconazole + caspofungin	41,199.20	0.73	56,758.82
Voriconazole + desoxycholate amphotericin B	39,838.48	0.69	57,590.02
Liposomal amphotericin B + voriconazole	43,667.17	0.60	72,652.36
Liposomal amphotericin B + caspofungin	42,262.27	0.57	74,445.10

Table 6: Outcomes 2018 model

It is remarkable that the difference in costs between the most and least expensive treatment is lower in this model (3829 euro) than in the baseline model (10,819 euro). The increase in costs and the lower difference in costs in the 2018 model can be explained either by the differences in costs used as input for the model (as can be seen in table 2) or by the inclusion of the costs for hematopoietic stem cell transplantation recipients. To distinguish between the two possible reasons, the costs have been plotted against the effects in figure 10. Panel A shows the baseline model, panel B the 2018 model and panel C shows the 2018 model without the costs for hematopoietic stem cell transplantation recipients. It can be seen that without the costs for hematopoietic stem cell transplantation recipients, the costs in the 2018 model do not differ much from those in the baseline model. As a result, by accounting for those costs, the predicted expenses rise for all treatment strategies.

Model	ICER Voriconazole + caspofungin vs Voriconazole + desoxycholate amphotericin B
Weibull	€ 40,711.03
Exponential	€ 53,061.98
Gompertz	€ 41,561.06
Loglogistic	€ 43,373.62
Preferred	€ 39,899.14

Table 7: Differences in ICERs in the 2018 model

Moreover, including the costs for hematopoietic stem cell transplantation recipients brings costs closer together, which can be explained as follows. The treatment strategies with Voriconazole as a first-line treatment are both more effective and less costly. Costs for hematopoietic stem cell transplantation recipients involve all costs that are not involved in treating invasive aspergillosis. Therefore, the more years (or days) lived, the higher those costs. This leads to the treatment strategies with respectively Voriconazole or Liposomal amphotericin B as first-line treatment to come close together. Based on this reasoning, the ICER to increase as well. Excluding costs for hematopoietic stem cell transplantation

recipients, but using 2018 prices, even makes the Voriconazole + Caspofungin marginally cheaper than the Voriconazole + Desoxycholate amphotericin B strategy, thereby dominating all other strategies.

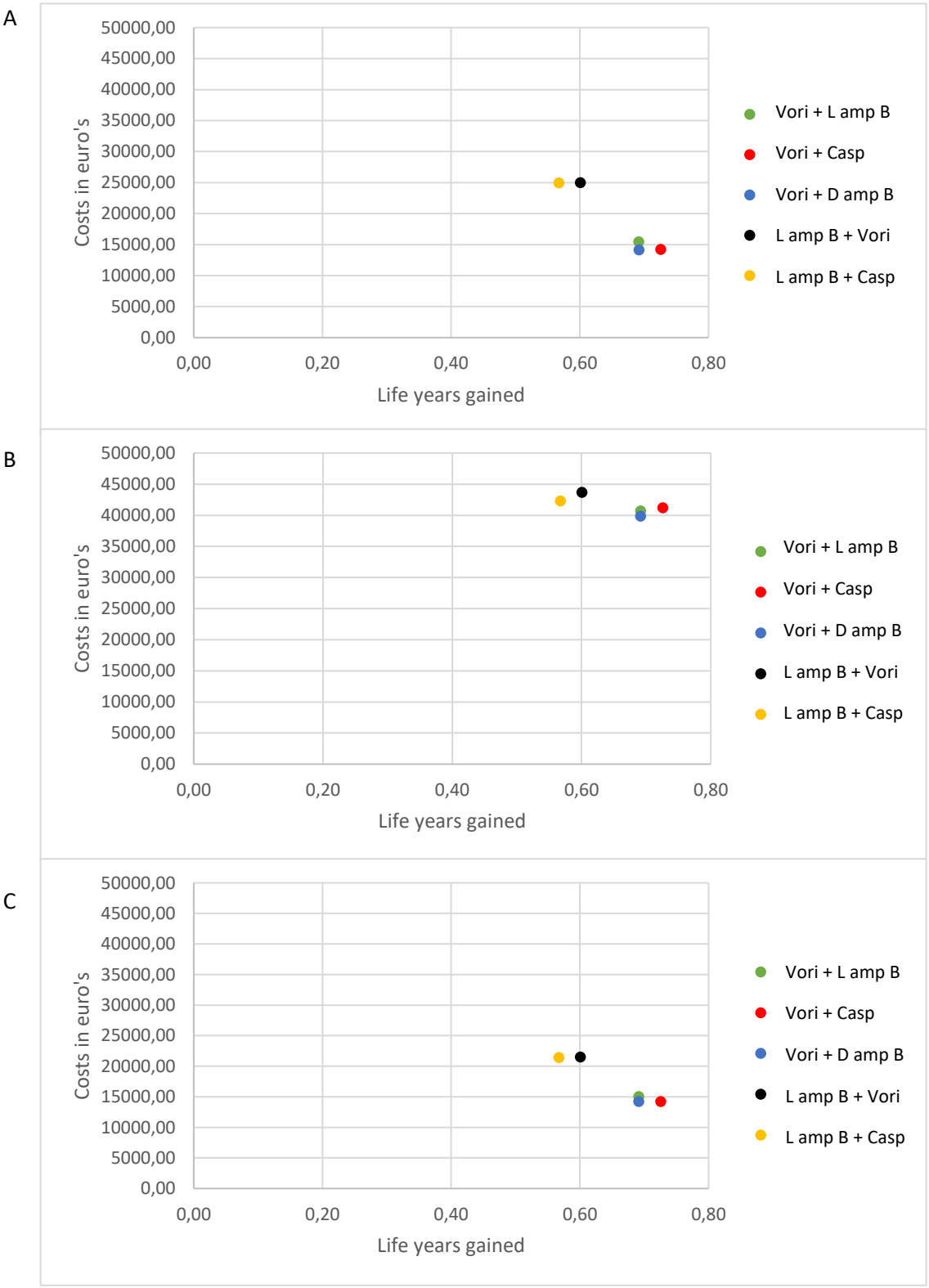

Figure 10: Cost-effectiveness analysis for A) baseline model B) 2018 model C) 2018 model without costs for hematopoietic stem cell transplantation recipients

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) is performed to take into account the uncertainty of the input parameters (Briggs et al., 2006). In our model there are actually two different kind of input parameters, namely costs and Gamma's and Lambda's for the different survival curves. It is important to choose the right distribution for each of the input parameters, in order to reflect the uncertainty underneath those values in a proper way. The probabilistic sensitivity analysis has been performed with the input parameters from the 2018 model, while it is important to assess the robustness of the model that will be used for health care decisions. Therefore, it is essential to use the most up to date information.

Costs can only take positive values, which needs to be reflected in the distribution which is chosen for the probabilistic sensitivity analysis. The most appropriate distribution for costs is the Gamma distribution, as this only allows values that are equal to or larger than zero (Briggs et al., 2006). For the gamma distribution, two parameters have to be estimated. The α is the shape parameter and is dependent on the mean and standard error of the particular variable. It can be calculated for variable x as follows: $\alpha = \text{mean}(x)^2/\text{se}(x)^2$. The β is the rate parameter and is calculated by: $\beta = \text{se}(x)^2/\text{mean}(x)$. For knowing the distribution, it is necessary to know or estimate the mean and the standard error. The mean is simply the value used in the deterministic analysis. However, the standard error has to be estimated. In this PSA, it is assumed that the standard error for the treatment costs is 10 percent of the mean (while certainty about prices is assumed to be fairly high), and the standard error for costs for adverse events, hospital costs and costs for hematopoietic stem cell transplant recipients are 20 percent (those costs are more uncertain).

Uncertainty around the survival curves is less straightforward to calculate, since the survival curves are all dependent on each other. Moreover, they have to be in a specific order. For example, per definition there must be more people alive then people who receive treatment. So, in our case, not only is there a high correlation between the survival curves, but they also must be in a specific order to avoid negative patient values in some groups. This makes it highly complicated to estimate uncertainty around the different survival curves. In this paper, uncertainty around both the gamma's and the lambda's of the different survival curves is estimated using a normal distribution with a standard error of 10 percent of the estimated value. As a result of the lack of real individual patient data, this standard error had to be estimated and it is therefore uncertain whether this standard error is an accurate representation of the actual uncertainty.

The PSA has been performed with running 1000 simulations. The associated cost-effectiveness acceptability curve is presented in figure 11. It shows that for each ICER threshold the probability that a particular strategy is cost-effective is about the same, except for a threshold of 40,000 euros. At this point, the probability that the strategies of Voriconazole and Caspofungin and Voriconazole and Desoxycholate amphotericin B are cost-effective, increases while this probability declines to almost 0 for the strategies with liposomal amphotericin B as first-line treatment. The most plausible explanation for this unusual result is that by allowing both the shape and the scale parameter of the different survival curves to change freely, survival curves cross each other which creates negative patient values in some simulation. The adjustments done to the survival curves as explained in the sub section "problems in distributions" are likely to no longer hold in some of the simulations. The result is an unreliable probabilistic sensitivity analysis.

One possible solution for the abovementioned problem is to allow only for uncertainty in the scale parameter, while keeping the shape parameter fixed. By doing this, the problem of survival curves crossing each other becomes smaller, but does not disappear entirely. As a result, the cost-effectiveness acceptability curve becomes more realistic, as can be seen in figure 12. It can be seen that a high threshold favors the most effective treatment strategy, which is as expected. However, at

any threshold, every treatment strategy has a change to be the most cost-effective one, which can also be observed in figure 15 where most treatment strategies overlap with each other. It might be possible that the results of this study are not robust or that the unusual results of this PSA are caused by not using real individual patient data.

A probabilistic sensitivity analysis, in which only the uncertainty concerning costs are included, was also performed. The respective cost-effectiveness acceptability curve is presented in figure 13. This figure shows that results are fairly robust regarding uncertainty in costs. Thereby, clearly differing from the other PSA's that have been performed. When the threshold is 30,000 euro or less, the Voriconazole and Desoxycholate amphotericin B is clearly superior, while at thresholds of 50,000 euro or higher the Voriconazole and Caspofungin strategy is the preferred strategy.

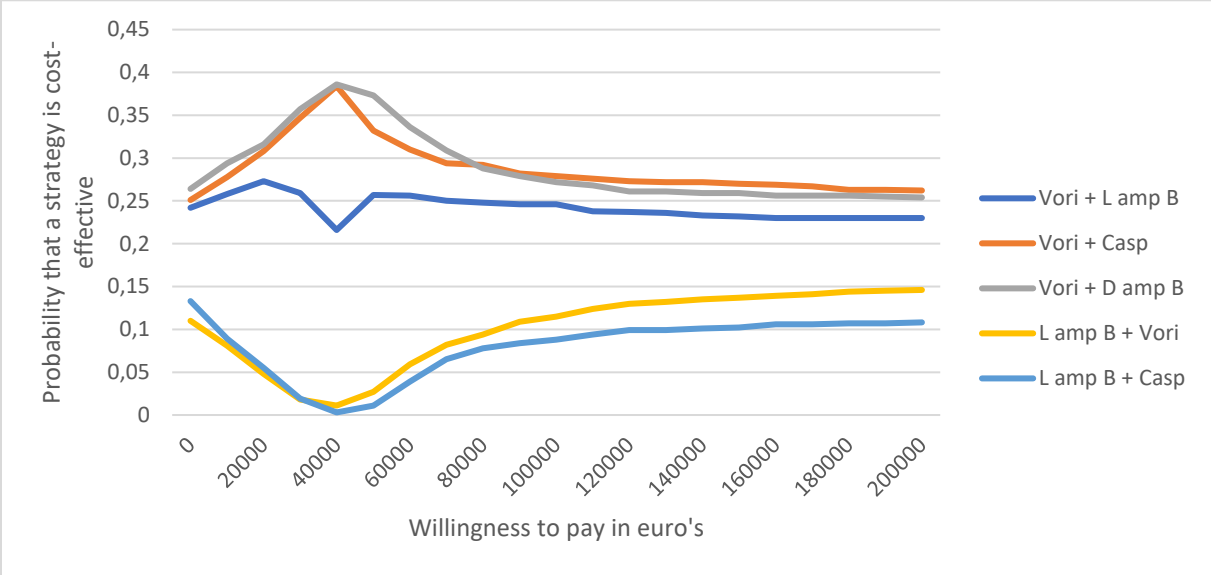

Figure 11: Cost-effectiveness acceptability curve full PSA

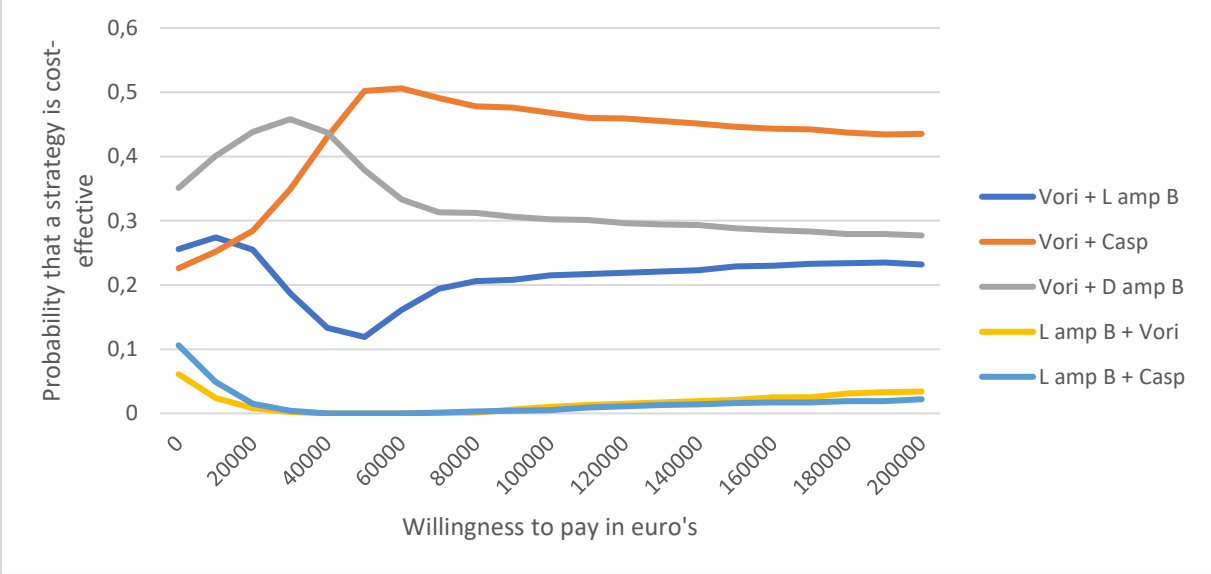

Figure 12: Cost-effectiveness acceptability curve PSA without uncertainty in the shape of survival curves

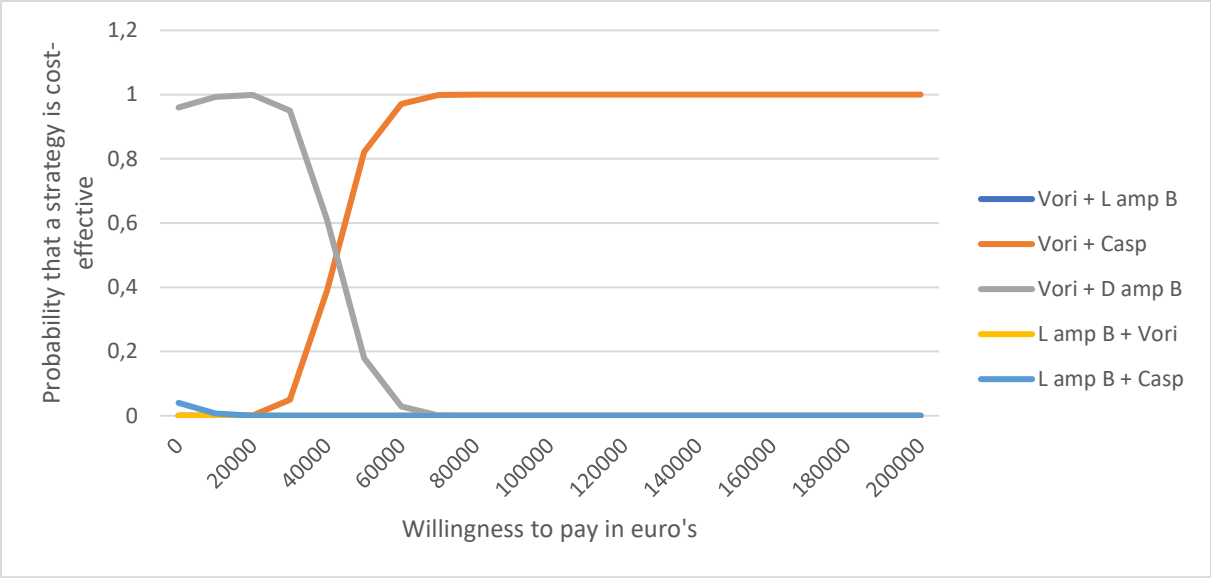

Figure 13: Cost-effectiveness acceptability curve PSA only with uncertainty around costs

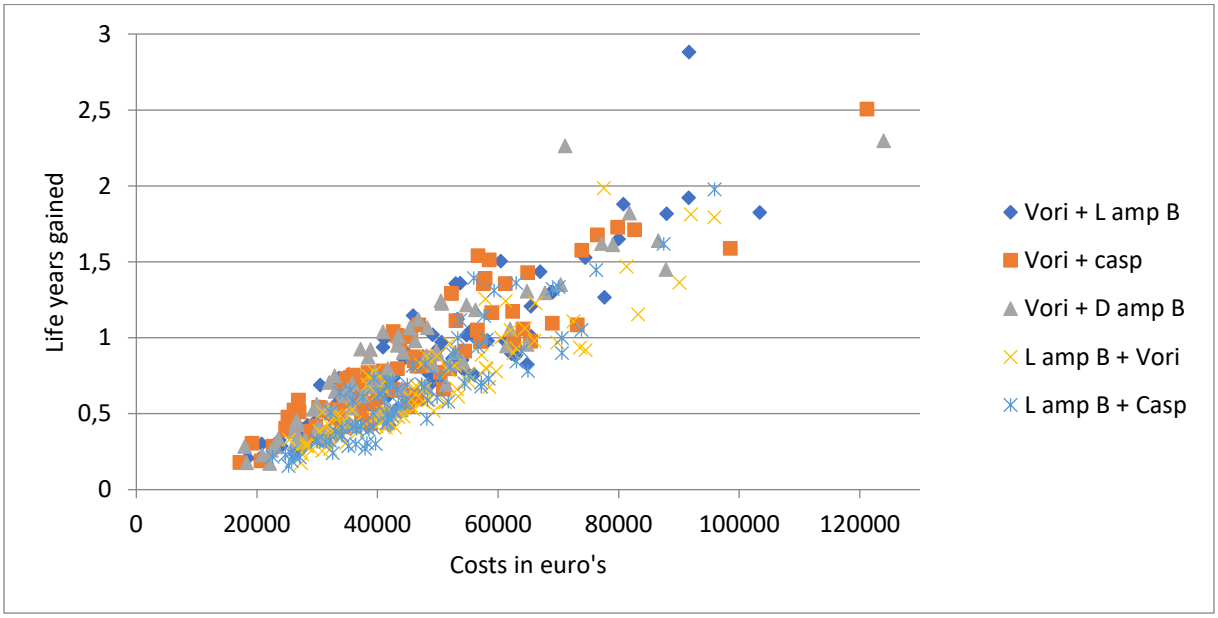

Figure 14: scatter diagram full PSA

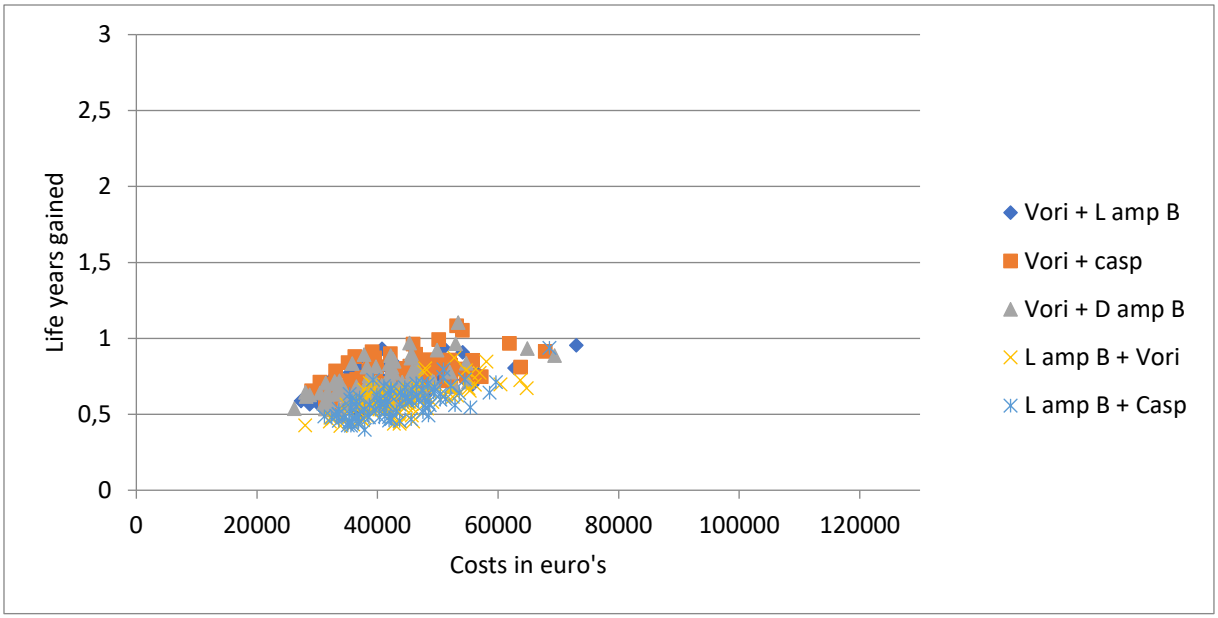

Figure 15: scatter diagram PSA without uncertainty shape of survival curves

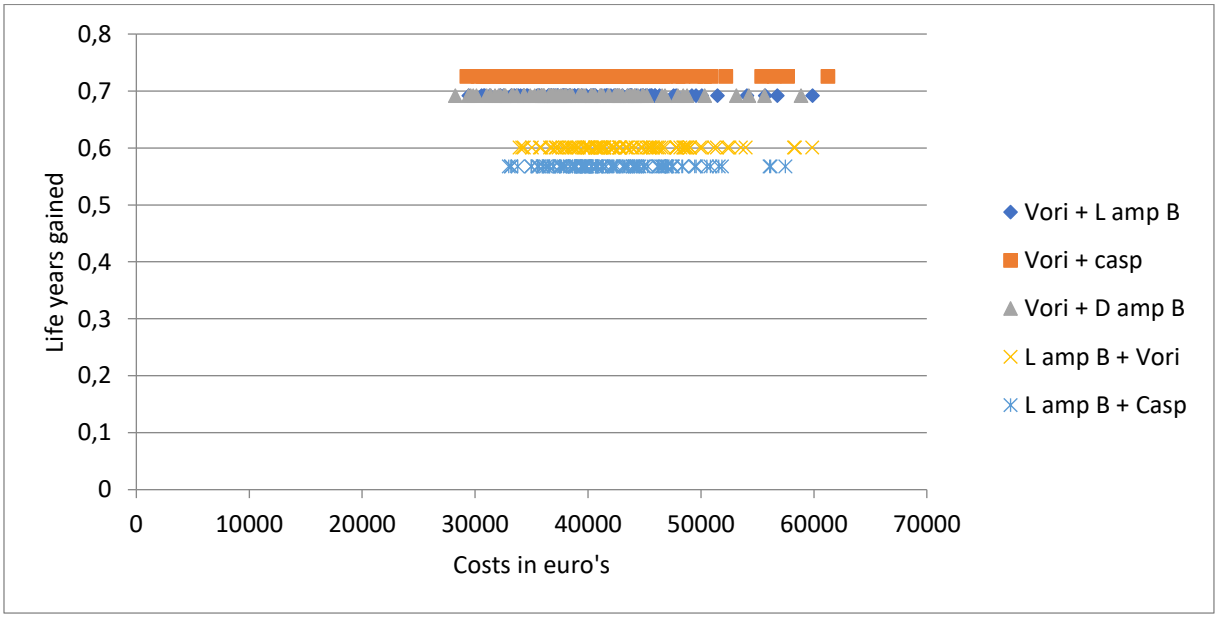

Figure 16: scatter diagram PSA only with uncertainty around costs

Discussion

This study has shown that it is feasible to build a Markov model for modelling the cost-effectiveness of different treatment strategies for invasive aspergillosis. However, the internal validity of the model is low, which mainly can be seen in the adjustments that had to be done in the survival analysis and in the unreliable results of the probabilistic sensitivity analysis.

This section will put the results of this study in a broader context. First, there will be a short discussion concerning the problems that emerged in the process of building the Markov model and whether those problems have been described in the literature. Next, the results of the model will be compared with both the study of Ament el al. (2007) and the current guidelines for the treatment of invasive aspergillosis. This will be followed by arguing what this study adds to the Health technology assessment literature. This section will then discuss the societal impact of this study. Finally, suggestions for further research will be given.

Problems with building the model

Part of the research goal was to investigate the feasibility of building a Markov model for invasive aspergillosis as being an acute illness. Therefore, it was important to reflect upon the process of building the model that is used in this study. The most important problems that came up involved incorporating costs, dealing with negative patient values and choosing the right distribution. Those topics will be discussed in this sub section.

The problem of negative patient values has, to my knowledge, not been described in literature, which suggests that it might be a consequence of not using real individual patient data and the very limited number of “observations”. Real individual patient data with daily observations will likely produce smoother Kaplan Meier curves which can more easily be fitted using parametric extrapolation and thereby solving this problem of negative patient values. However, such data was not available during this research. Moreover, the relatively small number of patients receiving second-line treatment or OLAT caused the different survival curves to be close to each other, which made it more likely for survival curves to cross. Another aspect is that the survival curves were estimated independently, while they are actually all dependent on each other. For example, the group patients on first-line treatment is a sub group of patients on treatment. Therefore, a possible solution could be to fit the curves dependent on each other. However, statistically, this would be challenging. Another possibility would be to run an individual (Monte Carlo) simulation. By simulating the path of each patient separately, negative patient values can per definition not exist, as in each cycle each patient is always in one of the health states (and only in one health state) (Briggs & Sculpher, 1998).

A well-known property of Markov models is that they do not have a memory (Drummond, 2015). This has a consequence for incorporating costs that depend on transitions between health states or on the total amount of patients that will go through a particular health state during the entire time horizon. Costs on adverse events are an example of the latter. While it is impossible to know the total amount of patients that, at some point of time, receive second-line treatment, it is also impossible to estimate how many patients will get adverse events from the second-line treatment. The same argument also applies to adverse events from OLAT. The solution of this paper to take the maximum amount of patients that are at a specific time point in the second-line treatment (or OLAT respectively) as an estimate will per definition lead to an underestimation for those costs. A different solution could be to separate those health states to patients that suffer and do not suffer from adverse events. Further research might use this approach, although it does add complexity while it is not certain that results will be more trustworthy.

The third difficulty in building the model was to use the right distribution to represent the survival curves in the model. In opposite to the previous problems, research was conducted on how to perform a survival analysis in a systematic manner (Latimer, 2013). This study has shown that for this patient population, different distributions have different characteristics and problems. As a result, no specific distribution is undoubtedly superior to either of the others. A systematic evaluation for the selection of the right distribution is therefore necessary (Latimer, 2013). It is advisable to publish the outcomes of the model with different distributions to show how robust results are regarding the different distributions. Manns et al. (2002) use a Markov model for a similar acute disease (severe sepsis) but do not explain which distribution they used for the survival analysis and why they selected that distribution. Our study provides an example on how the survival analysis as advised by Latimer (2013) can be executed.

Comparison of results with literature

This sub section will put the results of this study in a broader context. The outcomes of the baseline model will be compared with the outcomes of Ament et al. (2007). The outcomes of the 2018 model will be put in the context of the most recent guidelines on the treatment of invasive aspergillosis. The results of the probabilistic sensitivity analysis will not be compared with the literature, while those results are likely to be biased. However, there will be a discussion on what can explain the outcomes of the probabilistic sensitivity analysis.

While the same input parameters have been used in our model as in the decision tree in Ament, differences in results can be attributed to differences in the properties of the models. However, the results between the studies are quite similar. Treatments with voriconazole as first-line treatment are in both models dominant over treatments with Liposomal amphotericin B as first-line treatment. Moreover, Voriconazole + Caspofungin was in both studies the most effective treatment.

There were also differences between the studies. Costs were higher for every treatment strategy in our model. This can be explained by the fact that in the model of Ament et al. (2007) costs only occurred in the first 12 weeks, while in our model costs are endured over a much longer time period (5 years). Life years gained on the other hand were less in our model. In the model of Ament, everyone who survives after 12 weeks is expected to live another 2,2 years. Contrarily, in our Markov model, most patients die earlier. For most treatment strategies, percentage of survival after 1 year is around 20. This is a consequence of the dynamic inclusion of time in the Markov model, which makes these results more likely to represent the real-life situation. However, while data is transferred from the decision tree of Ament, those results are influenced by the lack of good individual patient data. Another difference between the results of both models is that Voriconazole + Desoxycholate amphotericin B was less expensive than Voriconazole + Caspofungin, which was the other way around in the decision tree of Ament et al. Consequently, Voriconazole + Caspofungin is not dominant over Voriconazole + Desoxycholate amphotericin B. The sub section titled scientific relevance will discuss the relevance of these differences in more detail.

The 2018 model shows that the Voriconazole + Desoxycholate amphotericin B is the least expensive treatment strategy. The only strategy that is more effective is the Voriconazole + Caspofungin strategy. The corresponding ICER is 39,899 euro. According to the health care institute of the Netherlands this ICER would be acceptable. As for severe illnesses the threshold is 50,000 euro per life year gained (Zwaap et al., 2015). Based on those results, it can be argued that Voriconazole + Caspofungin is the favored treatment strategy on in terms of cost-effectiveness. The most recent guidelines advise Voriconazole (either with or without Caspofungin) as first-line treatment. As second-line treatment, they advise Liposomal Amphotericin B or Isavuconazole (new tri azole which is on the market since 2015) (Kauffman et al., 2018). The guideline is based on clinical trials only. A recent cost-effectiveness

study by Harrington et al. (2017) showed that Isavuconazole was cost-effective compared with Voriconazole as first-line treatment. Their study used a decision tree instead of a Markov model.

As already mentioned in the results section, the unreliable results produced by the probabilistic sensitivity analysis can (at least partly) be explained by the existence of negative patient values, when allowing for uncertainty in the survival curves. This has two causes:

1. Data on which the survival curves are based are extrapolated from Ament. Based on a few observations, "individual patient data" is created, which causes unreliable estimates for the survival curves. This problem can easily be solved by using real individual patient data.
2. As already explained, there is a small amount of patients in the OLAT and second-line treatment groups, resulting in survival curves close to each other which makes it likely that when a probabilistic sensitivity analysis is being executed, these survival curves will frequently cross each other.

Further research with real individual patient data should clarify whether it is possible to perform a probabilistic sensitivity analysis that produces reliable results for this particular patient population. Manns et al. (2002) have successfully performed a probabilistic sensitivity analysis in their study regarding acute sepsis. Therefore, there is a good chance that this problem will be solved when real individual patient data is included. Another solution could be to perform individual simulation instead of cohort simulation. As explained above, by using individual simulation, per definition, no negative patient values can occur.

Scientific relevance

The differences in outcomes between our study and the study of Ament as mentioned above, suggest that it does matter whether a decision tree or Markov model is used. This holds while both studies use the same data. Therefore, it is important to make a well-founded decision on which model to use. Both models have different advantages and disadvantages. The structure of decision trees is apprehensible for health care professionals without much knowledge of health technology assessment. Furthermore, decision trees have a history, while branch probabilities can be assigned to each branch separately (Drummond, 2015). However, as previously mentioned, the main disadvantage of decision trees is that time is not explicitly defined within the model (Briggs et al., 2006). Time must be incorporated manually in the decision tree. Ament has assigned time values for every step, as can be seen in figure 2. However, switching probabilities are still time independent.

The main advantage of Markov models is that switching probabilities can be made time dependent, as has been done in this study. Clinical research has shown that, for example, the probability to die is much higher in the beginning of the illness than later in the course of the disease (see figure 8) (Barnes & Marr, 2007). Therefore, switching probabilities are in reality not time independent, and decision trees will give biased results. On the other hand, a disadvantage of Markov models is that they do not have a history. Because of this, some costs that are based on transitions cannot be reliably estimated. In our model, this was the case for adverse event costs in second-line treatment and OLAT. This can be overcome by adding extra health states, but at the cost of extra complexity (Briggs et al., 2006).

Above discussion implies that there is no perfect model and that a tradeoff between complexity and reliability of the model has to be made. There is no particular test or statistic to decide which model is appropriate for what kind of disease. However, while Markov models are frequently being used in chronic diseases as COPD (Menn et al., 2012), Alzheimer's disease (O'Brien et al., 1999), prostate cancer (Ramsay et al., 2015) and multiple sclerosis (Chilcott et al., 2003), the use of Markov models in

acute diseases is limited. To my knowledge, the study of Manns et al. (2002) about severe sepsis is the only study in which a Markov model is used in an economic evaluation for an acute illness.

The added value of our study over the study of Manns et al. is that this study shows how to systematically build a Markov model, based on the recommendations of both the ISPOR guidelines (Siebert et al., 2012) and the study of Latimer (2013). By explicitly mentioning the steps of building the model and addressing which assumptions are applicable for building the model, this paper can be used as an example on how to build a model for this particular patient population with appropriate individual patient data.

Societal relevance

Due to the nature of the data used it is not surprising that the results are similar to the results of Ament et al. (2007). However, by simply extracting the data of Ament to become individual patient data, those results should not be used for decision making. However, it can be seen that by updating the data of Ament to the prices of 2018, the most cost-effective strategy is still the Voriconazole + Caspofungin strategy. This implies that the conclusion that Voriconazole + Caspofungin is the preferred strategy, is robust.

Current guidelines advise that Voriconazole and Caspofungin should be combined as first-line treatment (Kauffman et al., 2018). This strategy has not been included in this model, as no data was available regarding this strategy. However, this treatment strategy should be included in future research.

Suggestions for further research

While the internal validity of this model is low due to the nature of the data used, it should be clear that the logical next step is to gain individual patient data for this patient population. When sufficient data is gathered, this study can be used as a guideline to build the model. There are two options on how data can be gathered, both with their advantages and disadvantages. Data can prospectively be collected by following how patients are treated in current practice. The other option is to collect data alongside a randomized controlled trial. Both options will be discussed here and what kind of data needs to be collected.

The first option is to collect data prospectively and thereby build a database without interfering in the decisions on which treatment is given. Hematopoietic stem cell transplant recipients where proven or probable invasive aspergillosis is diagnosed, should be included and followed during a period of 12 weeks. The following data should be collected:

- Which First-line (and if applicable second-line and OLAT) treatment they receive, for how long and the route of administration.
- Whether a patient dies within 12 weeks, and when he does, the day that he dies.
- Whether a patient has an adverse event from the treatment for which an intervention is needed.

Although this is the easiest way to fill a database, there are some disadvantages to this approach. First, while most patients will be treated according to the guidelines, one treatment strategy will be used much more than the others. Therefore, it will be hard to assure that there are enough observations for each treatment strategy. Second, by lack of randomization, results can be biased. This can happen, for example, when more severe ill patients receive different medication than less severe ill ones.

The other option is to collect data alongside a randomized controlled trial. Essentially, for the Markov model the same data is necessary as described above. Invasive aspergillosis is a relatively rare disease.

Yearly, in the Netherlands there are around 1200 hematopoietic stem cell transplantations (Passweg et al., 2016). Around 10 percent of the recipients get invasive aspergillosis, which means that the potential study population in the Netherlands in 120 patients per year. This means that not all the treatment strategies can be included in the study. Moreover, combination therapies are being used more often and Voriconazole and Caspofungin together is actually the recommended first-line treatment by the guidelines (Kauffman et al., 2018). Therefore, the following treatment strategies should be included in the trial:

- Voriconazole + Caspofungin
- Voriconazole + Desoxycholate amphotericin B
- Voriconazole/Caspofungin + Desoxycholate amphotericin B

Power calculations should determine how many patients should be included.

This approach will give more reliable results, but will be costlier and more complicated, while it likely has to be a multi-centre trial. This is due to the low incidence of invasive aspergillosis.

Conclusions

This final section will provide answers to the research questions stated in the introduction. The first research question was: “Based on cost-effectiveness, what is the preferred strategy in treating invasive aspergillosis in hematopoietic stem cell transplant recipients, taking into account that patients can switch at any time between health states?”

Based on this study the treatment strategy Voriconazole + Caspofungin is the most cost-effective strategy in treating invasive aspergillosis in hematopoietic stem cell transplant recipients. However, as already mentioned due to the lack of real individual patient data, data from Ament et al. (2007) has been used to create individual patient data. While this data is far from ideal, results are unreliable. Therefore, health care decisions should not be guided by the results of the study. Further research with real individual patient data is necessary to see whether the results of this study holds.

Voriconazole + Caspofungin was also the most cost-effective treatment strategy in the decision tree of Ament et al. (2007). However, some results have changed by using a Markov model. For example, in our study costs for all strategies were higher, life years gained for all strategies were lower and the treatment strategy Voriconazole + Desoxycholate amphotericin B was not dominated by Voriconazole + Caspofungin.

The second research question was the following: “What is the feasibility and additional value of using a Markov model (and thereby explicitly incorporating the time aspect) in economic evaluations on invasive aspergillosis in comparison to the fixed time definition imposed by decision trees?”

This study showed that it is feasible to build a Markov model for this particular study population. However, some problems emerged in the process of building the model. These include negative patient values in the Markov traces, incorporating costs that depend on transitions between health states or on the total amount of patients that will go through a particular health state during the entire time horizon and choosing the right distribution for the survival analysis. These problems can be solved, but it is important to mention and motivate the assumptions that have to be made. Moreover, gaining individual patient data might solve part of these problems.

The main advantage of using a Markov model is that, switching probabilities can be made time dependent, which is not possible in a decision tree. This should lead to more reliable results on the cost-effectiveness of the different treatment strategies, even in an acute disease as invasive aspergillosis. However, this comes at the costs of the additional problems that occur with making a Markov model as described above. Future research with real individual patient data should determine whether the benefits of the Markov model will outweigh the problems that come with it.

References

Ament, A., Hubben, M., Verweij, P., de Groot, R., Warris, A., & Donnelly, J. et al. (2007). Economic evaluation of targeted treatments of invasive aspergillosis in adult haematopoietic stem cell transplant recipients in the Netherlands: a modelling approach. Journal Of Antimicrobial Chemotherapy, 60(2), 385-393. http://dx.doi.org/10.1093/jac/dkm196

Barnes, P., & Marr, K. (2006). Aspergillosis: Spectrum of Disease, Diagnosis, and Treatment. Infectious Disease Clinics Of North America, 20(3), 545-561. http://dx.doi.org/10.1016/j.idc.2006.06.001

Barnes, P., & Marr, K. (2007). Risks, diagnosis and outcomes of invasive fungal infections in haematopoietic stem cell transplant recipients. British Journal Of Haematology, 139(4), 519-531. doi: 10.1111/j.1365-2141.2007.06812.x

Bitar, D., Lortholary, O., Le Strat, Y., Nicolau, J., Coignard, B., & Tattevin, P. et al. (2014). Population-Based Analysis of Invasive Fungal Infections, France, 2001–2010. Emerging Infectious Diseases, 20(7), 1163-1169. http://dx.doi.org/10.3201/eid2007.140087

Briggs, A., Sculpher, M., & Claxton, K. (2006). Decision modelling for health economic evaluation. OUP Oxford.

Briggs, A., & Sculpher, M. (1998). An introduction to Markov modelling for economic evaluation. Pharmacoeconomics, 13(4), 397-409.

Burnham, K., & Anderson, D. (2010). Model selection and multimodel inference (3rd ed.). New York: Springer.

Cadena, J., Thompson, G. R., & Patterson, T. F. (2016). Invasive Aspergillosis. Infectious Disease Clinics, 30(1), 125-142.

Carvalho-Dias, V., Sola, C., Cunha, C., Shimakura, S., Pasquini, R., & Queiroz-Telles, F. (2008). Invasive aspergillosis in hematopoietic stem cell transplant recipients: a retrospective analysis. Brazilian Journal Of Infectious Diseases, 12(5), 385-389. http://dx.doi.org/10.1590/s1413-86702008000500008

Cellini, S. R., & Kee, J. E. (2010). Cost-effectiveness and cost-benefit analysis. Handbook of practical program evaluation, 3.

Chilcott, J., Miller, D. H., McCabe, C., Tappenden, P., O'Hagan, A., Cooper, N. J., ... & Claxton, K. (2003). Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. Bmj, 326(7388), 522.

Collett, D. (2015). Modelling survival data in medical research. CRC press.

Denning, D. W. (1998). Invasive aspergillosis. Clinical infectious diseases, 781-803.

De Pauw, B., Walsh, T. J., Donnelly, J. P., Stevens, D. A., Edwards, J. E., Calandra, T., ... & Denning, D. W. (2008). Revised definitions of invasive fungal disease from the European organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. Clinical infectious diseases, 46(12), 1813-1821.

Drummond, M. (2015). Methods for the economic evaluation of health care programmes (4th ed.). Oxford University Press.

Fanos, V., & Cataldi, L. (2000). Amphotericin B-induced nephrotoxicity: a review. Journal of chemotherapy, 12(6), 463-470.

Gaieski, D. F., Edwards, J. M., Kallan, M. J., & Carr, B. G. (2013). Benchmarking the incidence and mortality of severe sepsis in the United States. Critical care medicine, 41(5), 1167-1174.

Harman, E. (2016). Aspergillosis: Practice Essentials, Background, Pathophysiology. Emedicine.medscape.com. Retrieved 14 September 2017, from http://emedicine.medscape.com/article/296052-overview#a2

Harrington, R., Lee, E., Yang, H., Wei, J., Messali, A., Azie, N., ... & Spalding, J. (2017). Cost-effectiveness analysis of isavuconazole vs. voriconazole as first-line treatment for invasive aspergillosis. Advances in therapy, 34(1), 207-220.

Herbrecht, R., Denning, D. W., Patterson, T. F., Bennett, J. E., Greene, R. E., Oestmann, J. W., ... & Sylvester, R. (2002). Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. New England Journal of Medicine, 347(6), 408-415.

Hwang, J. S., & Wang, J. D. (1999). Monte Carlo estimation of extrapolation of quality-adjusted survival for follow-up studies. Statistics in medicine, 18(13), 1627-1640.

Jansen, J., Meis, J., Blijlevens, N., & van't Wout, J. (2005). Economic evaluation of voriconazole in the treatment of invasive aspergillosis in the Netherlands. Current Medical Research And Opinion, 21(10), 1535-1546. http://dx.doi.org/10.1185/030079905x65312

Karthaus, M. (2011). Prophylaxis and treatment of invasive aspergillosis with voriconazole, posaconazole and caspofungin - review of the literature. European Journal Of Medical Research, 16(4), 145. http://dx.doi.org/10.1186/2047-783x-16-4-145

Kauffman, C., & Gregg, K. (2015). Invasive Aspergillosis: Epidemiology, Clinical Aspects, and Treatment. Seminars In Respiratory And Critical Care Medicine, 36(05), 662-672. http://dx.doi.org/10.1055/s-0035-1562893

Kauffman, C., Sexton, D., & Thorner, A. (2017). Diagnosis of invasive aspergillosis. Retrieved from https://www.uptodate.com/contents/diagnosis-of-invasive-aspergillosis

Kauffman, C., Sexton, D., & Thorner, A. (2018). Treatment and prevention of invasive aspergillosis. Retrieved from https://www.uptodate.com/contents/treatment-and-prevention-of-invasive-aspergillosis

Kontoyiannis, D., Marr, K., Park, B., Alexander, B., Anaissie, E., & Walsh, T. et al. (2010). Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clinical Infectious Diseases, 50(8), 1091-1100. http://dx.doi.org/10.1086/651263

Latimer, N. (2013). Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data. School of Health and Related Research, University of Sheffield, UK.

Maertens, J. A., Raad, I. I., Marr, K. A., Patterson, T. F., Kontoyiannis, D. P., Cornely, O. A., & Baddley, J. W. et al. (2016). Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. The Lancet, 387(10020), 760-769.

Manns, B. J., Lee, H., Doig, C. J., Johnson, D., & Donaldson, C. (2002). An economic evaluation of activated protein C treatment for severe sepsis. New England Journal of Medicine, 347(13), 993-1000.

Marr, K. A., Boeckh, M., Carter, R. A., Kim, H. W., & Corey, L. (2004). Combination antifungal therapy for invasive aspergillosis. Clinical infectious diseases, 39(6), 797-802.

Marr, K., Carter, R., Boeckh, M., Martin, P., & Corey, L. (2002). Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood, 100(13), 4358-4366. doi: 10.1182/blood-2002-05-1496

Marr, K. A., Schlamm, H. T., Herbrecht, R., Rottinghaus, S. T., Bow, E. J., Cornely, O. A., & Lee, D. G. et al. (2015). Combination Antifungal Therapy for Invasive Aspergillosis A Randomized Trial: Combination Therapy for Invasive Aspergillosis. Annals of internal medicine, 162(2), 81-89.

Marr, K. A. (2015). Epidemiology and clinical manifestations of invasive aspergillosis. UpToDate. Waltham (MA).

Marr, K. A. (2017). Treatment and prevention of invasive aspergillosis. UpToDate. Waltham (MA).

Menn, P., Leidl, R., & Holle, R. (2012). A lifetime Markov model for the economic evaluation of chronic obstructive pulmonary disease. Pharmacoeconomics, 30(9), 825-840.

Morgan, J., Wannemuehler, K. A., Marr, K. A., Hadley, S., Kontoyiannis, D. P., Walsh, T. J., & Warnock, D. W. et al. (2005). Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program. Medical mycology, 43(sup1), 49-58.

O'brien, B. J., Goeree, R., Hux, M., Iskedjian, M., Blackhouse, G., Gagnon, M., & Gauthier, S. (1999). Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. Journal of the American Geriatrics Society, 47(5), 570-578.

Passweg, J. R., Baldomero, H., Bader, P., Bonini, C., Cesaro, S., Dreger, P., ... & Gennery, A. (2016). Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. Bone marrow transplantation, 51(6), 786.

Patterson, T., Thompson, G., Denning, D., Fishman, J., Hadley, S., & Herbrecht, R. et al. (2016). Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases, 63(4), e1-e60. http://dx.doi.org/10.1093/cid/ciw326

Paulussen, C., Hallsworth, J. E., Álvarez-Pérez, S., Nierman, W. C., Hamill, P. G., Blain, D., ... & Lievens, B. (2017). Ecology of aspergillosis: insights into the pathogenic potency of Aspergillus fumigatus and some other Aspergillus species. Microbial biotechnology, 10(2), 296-322.

Perea, J. A., de Rada, B. S. D., Quetglas, E. G., & Juarez, M. M. (2004). Oral versus intravenous therapy in the treatment of systemic mycosis. Clinical Microbiology and Infection, 10, 96-106.

Ramsay, C. R., Adewuyi, T. E., Gray, J., Hislop, J., Shirley, M. D., Jayakody, S., ... & N'Dow, J. (2015). Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England), 19(49), 1.

Saito, A., Cutler, C., Zahrieh, D., Soiffer, R., Ho, V., & Alyea, E. et al. (2008). Costs of Allogeneic Hematopoietic Cell Transplantation with High-Dose Regimens. Biology Of Blood And Marrow Transplantation, 14(2), 197-207. http://dx.doi.org/10.1016/j.bbmt.2007.10.010

Siebert, U., Alagoz, O., Bayoumi, A., Jahn, B., Owens, D., Cohen, D., & Kuntz, K. (2012). State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Value In Health, 15(6), 812-820. http://dx.doi.org/10.1016/j.jval.2012.06.014

Thompson, G., & Lat. (2011). Update on the optimal use of voriconazole for invasive fungal infections. Infection And Drug Resistance, 4, 43-53. http://dx.doi.org/10.2147/idr.s12714

Van der Linden, J. W. M., Arendrup, M. C., Warris, A., Lagrou, K., Pelloux, H., Hauser, P. M., & Dannaoui, E. et al. (2015). Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus. Emerging infectious diseases, 21(6), 1041.

Wingard, J., Herbrecht, R., Mauskopf, J., Schlamm, H., Marciniak, A., & Roberts, C. (2007). Resource use and cost of treatment with voriconazole or conventional amphotericin B for invasive aspergillosis. Transplant Infectious Disease, 9(3), 182-188. http://dx.doi.org/10.1111/j.1399-3062.2007.00210.x

Wingard, J., Kauffman, C., & Thorner, A. (2018). Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients. Retrieved from https://www.uptodate.com/contents/prophylaxis-of-invasive-fungal-infections-in-adult-hematopoietic-cell-transplant-recipients

Zwaap, J., Knies, S., Van der Meijden, C., & Staal, P. (2015). Kosteneffectiviteit in de praktijk. Zorginstituut Nederland.