Pharmacokinetics and optimal exposure of antifungal drugs in critically ill patients

van der Elst, Kimberly Corina Maria

Chapter 9

General discussion & future perspectives

In this thesis we have evaluated the pharmacokinetics and the exposure of antifungal drugs in critically ill adults and children. We have shown that insufficient antifungal drug exposure is common in critically ill patients and that the standard dose, recommended in the Summary of Product Characteristics, is often inadequate for this patient group.

9.1 Critically ill pediatric patients

In Chapter 2 we have shown that pediatric cancer patients do not achieve an adequate exposure to fluconazole with the currently recommended dosing regimen and that a higher fluconazole concentration was associated with a shorter time to culture conversion [1]. Over the past 5.5 years, *Candida* species were cultured in 1248 children in the University Medical Center Groningen. In 94% of the cases, the *Candida* isolate was susceptible to fluconazole. The average costs for intravenous treatment with fluconazole were €28 per patient per day (2014). If the treatment with fluconazole fails, more expensive second line antifungal agents, such as amphotericin B (€145 - €290 per day) or caspofungin (€420 per day), are used for the treatment of invasive candidiasis (IC). With the determination of an optimal fluconazole dose, an adequate treatment with fluconazole can be achieved and hence there is no need to divert to more expensive second line antifungal agents. Furthermore, mortality significantly increases in patients with candidemia if there is a delay in the initiation of adequate fluconazole therapy, and an inadequate fluconazole dose is associated with an increased hospital stay and costs [2, 3]. Adequate exposure to fluconazole is therefore essential for an effective treatment and hence for a better outcome of the treatment, potentially leading to a reduced hospital stay. A prospective dose-finding study of fluconazole in pediatric cancer patients should be carried out to determine a more appropriate fluconazole dose and to ensure adequate fluconazole exposure in these patients. Fluconazole is a powerful and cheap drug and it is the primary therapy in children with IC. Provided that dose adjustments are made for specific patient groups, such as cancer patients, fluconazole is still a good choice for the treatment of IC in children and infants.

In Chapter 2 we have shown that it is important to evaluate the treatment with antifungal drugs in children. Children are typically not included in registration studies by the manufacturer of the drug due to ethical problems and technical challenges. As a result, many drugs have not been approved for the use in children, and drugs are often used outside the terms of the product's approval (off-label use). Indeed, almost half of the drugs prescribed in a children's hospital in the Netherlands were unapproved for the use in children [4]. Since children clearly need the treatment, the recommended childrens dose is extrapolated from the adult dose, which may result in decreased efficacy or toxic effects. To overcome the above-mentioned challenges, observational studies could be very useful to evaluate the drug exposure and to collect data on the treatment when (new) drugs are administered to children. Based on the collected data, the treatment can be optimized and childrens dosing recommendations could be made without extensive clinical trials. Besides, with the development of noninvasive sampling methods, such as oral fluid and dried blood spot (DBS) analysis, pharmacokinetic studies and Therapeutic Drug Monitoring (TDM) are much less burdening, and can therefore easier be performed in children.

9.2 Patients on the intensive care unit

In critically ill adults, the echinocandins (such as caspofungin) are recommended as primary therapy for IC. Furthermore, caspofungin is recommended as empirical treatment for suspected IC in this patient population [5]. In Chapter 8, we have shown that the caspofungin exposure in patients on the intensive care unit (ICU) was low compared with the exposure in healthy volunteers and other (non-) critically ill patients, most likely as a result of a larger volume of distribution. Furthermore, the exposure was low in patients of certain weight categories and in patients suffering from severe liver damage who received a reduced caspofungin dose. Our findings suggest that these patients should perhaps initially receive a higher empiric maintenance dose. Since a delay in empirical treatment is a potential risk factor for mortality [6], it is important to provide early appropriate treatment and to achieve adequate exposure early after the start of the treatment. Our findings, as well as previously published case reports [7,8], were all in ICU patients and these findings have not yet been confirmed in other patient groups, such as patients with hematological malignancies. Further research is needed to provide evidence for the development of new dosing recommendations. With these dosing recommendations, and subsequent TDM in certain cases, adequate exposure can be achieved shortly after the start of the treatment with caspofungin in ICU patients.

Our study showed that it is important to perform pharmacokinetic studies and

to evaluate the exposure of drugs in critically ill patients since the pharmacokinetics and hence the plasma concentration of a drug can be influenced by altered drug absorption, distribution, metabolism, and clearance in this patient group [9–14]. Since most patients on the ICU have a central venous catheter, blood sampling to obtain full pharmacokinetic curves can relatively easy be performed in these patients. It is important to start observational pharmacokinetic studies as soon as new drugs are introduced in this patient group. If the exposure appears insufficient, prospective dose finding studies should be performed to develop more appropriate dosing regimens for patients on the ICU.

9.3 Immunocompromised patients

In Chapter 4 we have demonstrated that the posaconazole exposure was not sufficient in over 40% of patients with invasive fungal disease (IFD), or those at risk for IFD, after administration of the oral suspension. Furthermore, a higher posaconazole concentration was associated with improved outcome. Based on the results of our study and other recent findings, we recommend that the posaconazole oral suspension is not prescribed to patients who are unable to eat or use a proton pump inhibitor/H_2-antagonist [15–22]. The gastro-resistant tablet or the intravenous formulation that has recently entered the market, are more suitable for these patients. An adequate exposure is reached with both formulations in a once daily dose compared to the oral suspension, which requires dosing between two and four times daily [23–26]. Since the tablet cannot be crushed or chewed, the oral suspension will remain a treatment option for patients who are unable to take tablets. Posaconazole is used as salvage therapy for invasive aspergillosis, with only few other alternatives left, and it is used for the treatment of specific and life threatening IFD, such as zygomycosis [27, 28]. Optimizing the posaconazole exposure in these patients is important for survival. Besides, posaconazole has been associated with an improved safety profile compared to voriconazole and concentration-dependent adverse events have not been identified to date [24]. The different posaconazole formulations, in combination with TDM in case of the oral suspension [29, 30], can help to ensure sufficient posaconazole exposure and these factors taken together make posaconazole a valuable addition to the antifungal prophylaxis and treatment arsenal.

9.4 Therapeutic Drug Monitoring

Critically ill patients often have complex and multiple pathologies while they receive multiple pharmacotherapeutic and other interventions. The pharmacoki-

netics of antifungal drugs can therefore be influenced and unpredictable and the required antifungal drug exposure may not be reached. Besides the development of new dosing strategies for critically ill patients, TDM can be useful to ensure that patients achieve target drug concentrations while toxicity is prevented [9,10]. TDM of voriconazole, posaconazole, itraconazole, and flucytosine may improve treatment outcome with reduced toxicity; TDM is therefore recommended in the guidelines for the treatment of IFD [5,29,31–37]. For fluconazole and caspofungin, TDM may have added value for the treatment. TDM can help to ensure timely target attainment in critically ill (pediatric) patients who are at risk of under-exposure. Preferably, new dosing recommendations should be developed for these patients, reducing the need for TDM. However, TDM remains important in critically ill adults and children who do not respond adequately to the antifungal therapy, who have infections at sanctuary sites (e.g. central nervous system), who have an infection with an organism with a reduced susceptibility, in patients with disease carrying a poor prognosis, in case of drug-drug interactions; and if toxicity is suspected [30,38]. Prospective randomized clinical trials should be carried out to determine if therapeutic interventions aiming at optimizing drug exposure, result in an improved treatment outcome.

To facilitate TDM of antifungal drugs, we have developed noninvasive sampling methods for performing TDM, such as an oral fluid analysis for fluconazole in pediatric patients (Chapter 3) and a DBS analysis for the azoles in adult patients (Chapter 5) [39,40]. Oral fluid sampling is a noninvasive, painless alternative to perform TDM in children when blood sampling is not possible or desirable and it is preferred over blood sampling by the majority of the patients and their parents [41]. DBS was advantageous in that sampling was significantly less painful, and DBS can be performed at home, saving time traveling to the hospital for blood sampling [40]. With oral fluid and DBS analysis, the possibilities of TDM of the triazoles can be extended to patients at home and to hospitals without an advanced bioanalytical infrastructure. Furthermore, these methods can be used in research in children and adults where venous blood sampling is not possible or not desirable.

9.5 Therapeutic drug management

To ensure adequate treatment, the exposure of the antifungal drug needs to be sufficient. Besides the exposure, the susceptibility of the organism is equally important to reach the required pharmacokinetic and pharmacodynamic (PK/PD) target. *In vivo* studies have demonstrated that the area under the concentration-time curve (AUC) over 24 hours to the minimum inhibitory concentration (MIC) is a good descriptor of the fluconazole and echinocandin exposure-response relationship [42–44]. Our studies showed that the antifungal drug exposure in critically

ill patients was low, however, if MIC values are low as well, the AUC/MIC target can still be reached with lower AUC values. It is therefore important to know the AUC/MIC, not only to establish adequate exposure, but also to avoid unnecessary dose escalations, thereby avoiding possible side effects. Furthermore, antifungal resistance is increasing and infections with isolates with elevated MICs are associated with poorer outcomes and breakthrough infections during antifungal treatment and prophylaxis [36, 45–47]. Antifungal drug susceptibility testing is therefore an essential component to guide therapeutic decision-making and to optimize the antifungal treatment while reducing the emergence of antifungal resistance.

9.6 Final remarks

With the increasing number of immunocompromised and critically patients, the incidence of IFD such as candidemia and invasive aspergillosis has increased in recent years [48]. Antifungal treatment has improved survival in these patients, however, mortality due to IFD has remained high with the currently used antifungal dosing regimens [33, 49–60]. Too often, the antifungal drug exposure in critically ill adults and children is inadequate with the standard dose. These findings call for the development of a more personalized therapy for patients with IFD. This treatment should be based on the characteristics of the fungus (type, MIC, location) and on the characteristics of the patient (underlying disease, and treatment of the disease, leading to altered absorption, distribution, metabolism, or clearance of the drug). Together, the characteristics of the fungus and the patient provide information on the appropriate antifungal treatment for the individual patient in the optimal dose, thereby avoiding unnecessary, ineffective, or toxic therapy [61]. With this strategy, adequate antifungal treatment can be achieved with the current arsenal of antifungal drugs [62].

In conclusion, it is important to investigate the pharmacokinetics and exposure of antifungal drugs in critically ill adults and children and establish the optimal dose for these patient groups. Adequate initial dosing regimens and subsequent TDM are needed to ensure a fast and adequate drug exposure and to attain the required PK/PD target in the critically ill patient, resulting in an improved efficacy and safety of the antifungal treatment and to a better outcome of the treatment of invasive fungal infections.

Bibliography

[1] K. C. van der Elst, M. Pereboom, E. R. van den Heuvel, J. G. Kosterink, E. H. Scholvinck, and J. W. Alffenaar, "Insufficient fluconazole exposure in pediatric cancer patients and the need for therapeutic drug monitoring in critically ill children," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **59**, pp. 1527–1533, Dec 1 2014.

[2] K. W. Garey, M. Rege, M. P. Pai, D. E. Mingo, K. J. Suda, R. S. Turpin, and D. T. Bearden, "Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **43**, pp. 25–31, Jul 1 2006.

[3] K. W. Garey, R. S. Turpin, D. T. Bearden, M. P. Pai, and K. J. Suda, "Economic analysis of inadequate fluconazole therapy in non-neutropenic patients with candidaemia: a multi-institutional study," *International journal of antimicrobial agents* **29**, pp. 557–562, May 2007.

[4] G. W. 't Jong, A. G. Vulto, M. de Hoog, K. J. Schimmel, D. Tibboel, and J. N. van den Anker, "A survey of the use of off-label and unlicensed drugs in a dutch children's hospital," *Pediatrics* **108**, pp. 1089–1093, Nov 2001.

[5] P. G. Pappas, C. A. Kauffman, D. Andes, D. K. B. Jr, T. F. Calandra, J. E. E. Jr, S. G. Filler, J. F. Fisher, B. J. Kullberg, L. Ostrosky-Zeichner, A. C. Reboli, J. H. Rex, T. J. Walsh, J. D. Sobel, and I. D. S. of America, "Clinical practice guidelines for the management of candidiasis: 2009 update by the infectious diseases society of america," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **48**, pp. 503–535, Mar 1 2009.

[6] M. Morrell, V. J. Fraser, and M. H. Kollef, "Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality," *Antimicrobial Agents and Chemotherapy* **49**, pp. 3640–3645, Sep 2005.

[7] K. C. van der Elst, R. J. Bruggemann, M. G. Rodgers, and J. W. Alffenaar, "Plasma concentrations of caspofungin at two different dosage regimens in a patient with hepatic dysfunction," *Transplant infectious disease : an official journal of the Transplantation Society* , Feb 9 2012.

[8] I. Spriet, W. Meersseman, P. Annaert, J. de Hoon, and L. Willems, "Pharmacokinetics of caspofungin in a critically ill patient with liver cirrhosis," *European journal of clinical pharmacology* **67**, pp. 753–755, Jul 2011.

[9] T. W. Felton, W. W. Hope, and J. A. Roberts, "How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it?," *Diagnostic microbiology and infectious disease* **79**, pp. 441–447, Aug 2014.

[10] F. Pea, P. Viale, and M. Furlanut, "Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability," *Clinical pharmacokinetics* **44**(10), pp. 1009–1034, 2005.

[11] B. M. Power, A. M. Forbes, P. V. van Heerden, and K. F. Ilett, "Pharmacokinetics of drugs used in critically ill adults," *Clinical pharmacokinetics* **34**, pp. 25–56, Jan 1998.

[12] B. S. Smith, D. Yogaratnam, K. E. Levasseur-Franklin, A. Forni, and J. Fong, "Introduction to drug pharmacokinetics in the critically ill patient," *Chest* **141**, pp. 1327–1336, May 2012.

[13] A. A. Udy, J. A. Roberts, and J. Lipman, "Clinical implications of antibiotic pharmacokinetic principles in the critically ill," *Intensive care medicine* **39**, pp. 2070–2082, Dec 2013.

[14] U. Theuretzbacher, "Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **54**, pp. 1785–1792, Jun 2012.

[15] M. J. Dolton, J. E. Ray, S. C. Chen, K. Ng, L. Pont, and A. J. McLachlan, "A multi-center study of posaconazole therapeutic drug monitoring: Exposure-response and factors affecting concentration," *Antimicrobial Agents and Chemotherapy* , Aug 13 2012.

[16] M. Vaes, M. Hites, F. Cotton, A. M. Bourguignon, M. Csergo, C. Rasson, L. Ameye, D. Bron, F. Jacobs, and M. Aoun, "Therapeutic drug monitoring of posaconazole in patients with acute myeloid leukemia or myelodysplastic syndrome," *Antimicrobial Agents and Chemotherapy* **56**, pp. 6298–6303, Dec 2012.

[17] P. Cojutti, A. Candoni, E. Simeone, L. Franceschi, R. Fanin, and F. Pea, "Antifungal prophylaxis with posaconazole in patients with acute myeloid leukemia: dose intensification coupled with avoidance of proton pump inhibitors is beneficial in shortening time to effective concentrations," *Antimicrobial Agents and Chemotherapy* **57**, pp. 6081–6084, Dec 2013.

[18] M. R. Crombag, C. Huisman, E. M. Kemper, R. J. Bruggemann, and Y. A. Bijleveld, "Posaconazole treatment in hematology patients: a pilot study of therapeutic drug monitoring," *Therapeutic drug monitoring* **34**, pp. 320–325, Jun 2012.

[19] J. W. Alffenaar, S. van Assen, T. S. van der Werf, J. G. Kosterink, and D. R. Uges, "Omeprazole significantly reduces posaconazole serum trough level," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **48**, p. 839, Mar 15 2009.

[20] M. J. Dolton, R. J. Bruggemann, D. M. Burger, and A. J. McLachlan, "Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis," *Antimicrobial Agents and Chemotherapy* , Sep 8 2014.

[21] C. Eiden, J. C. Meniane, H. Peyriere, S. Eymard-Duvernay, G. L. Falher, P. Ceballos, N. Fegueux, M. Cociglio, J. Reynes, and D. Hillaire-Buys, "Therapeutic drug monitoring of posaconazole in hematology adults under posaconazole prophylaxis: influence of food intake," *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* **31**, pp. 161–167, Feb 2012.

[22] G. Krishna, A. Moton, L. Ma, M. M. Medlock, and J. McLeod, "Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers," *Antimicrobial Agents and Chemotherapy* **53**, pp. 958–966, Mar 2009.

[23] G. Krishna, L. Ma, M. Martinho, R. A. Preston, and E. O'Mara, "A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers," *The Journal of antimicrobial chemotherapy* **67**, pp. 2725–2730, Nov 2012.

[24] M. J. Dolton and A. J. McLachlan, "Optimizing azole antifungal therapy in the prophylaxis and treatment of fungal infections," *Current opinion in infectious diseases* **27**, pp. 493–500, Dec 2014.

[25] J. Maertens, O. A. Cornely, A. J. Ullmann, W. J. Heinz, G. Krishna, H. Patino, M. Caceres, N. Kartsonis, H. Waskin, and M. N. Robertson, "Phase 1b study of the pharmacokinetics and safety of posaconazole intravenous solution in patients at risk for invasive fungal disease," *Antimicrobial Agents and Chemotherapy* **58**, pp. 3610–3617, Jul 2014.

[26] D. S. Jung, F. P. Tverdek, and D. P. Kontoyiannis, "Switching from posaconazole suspension to tablets increases serum drug levels in leukemia patients without clinically relevant hepatotoxicity," *Antimicrobial Agents and Chemotherapy* **58**, pp. 6993–6995, Nov 2014.

[27] J. A. van Burik, R. S. Hare, H. F. Solomon, M. L. Corrado, and D. P. Kontoyiannis, "Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **42**, pp. e61–5, Apr 1 2006.

[28] R. N. Greenberg, K. Mullane, J. A. van Burik, I. Raad, M. J. Abzug, G. Anstead, R. Herbrecht, A. Langston, K. A. Marr, G. Schiller, M. Schuster, J. R. Wingard, C. E. Gonzalez, S. G. Revankar, G. Corcoran, R. J. Kryscio, and R. Hare, "Posaconazole as salvage therapy for zygomycosis," *Antimicrobial Agents and Chemotherapy* **50**, pp. 126–133, Jan 2006.

[29] M. J. Dolton, J. E. Ray, D. Marriott, and A. J. McLachlan, "Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring," *Antimicrobial Agents and Chemotherapy* **56**, pp. 2806–2813, Jun 2012.

[30] H. R. Ashbee, R. A. Barnes, E. M. Johnson, M. D. Richardson, R. Gorton, and W. W. Hope, "Therapeutic drug monitoring (tdm) of antifungal agents: guidelines from the british society for medical mycology," *The Journal of antimicrobial chemotherapy* **69**, pp. 1162–1176, May 2014.

[31] H. R. Ashbee, R. A. Barnes, E. M. Johnson, M. D. Richardson, R. Gorton, and W. W. Hope, "Therapeutic drug monitoring (tdm) of antifungal agents: guidelines from the british society for medical mycology," *The Journal of antimicrobial chemotherapy* , Dec 29 2013.

[32] T. J. Walsh, E. J. Anaissie, D. W. Denning, R. Herbrecht, D. P. Kontoyiannis, K. A. Marr, V. A. Morrison, B. H. Segal, W. J. Steinbach, D. A. Stevens, J. A. van Burik, J. R. Wingard, T. F. Patterson, and I. D. S. of America, "Treatment of aspergillosis: clinical practice guidelines of the infectious diseases society of america," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **46**, pp. 327–360, Feb 1 2008.

[33] W. W. Hope, E. Castagnola, A. H. Groll, E. Roilides, M. Akova, M. C. Arendrup, S. Arikan-Akdagli, M. Bassetti, J. Bille, O. A. Cornely, M. Cuenca-Estrella, J. P. Donnelly, J. Garbino, R. Herbrecht, H. E. Jensen, B. J. Kullberg, C. Lass-Florl, O. Lortholary, W. Meersseman, G. Petrikkos, M. D. Richardson, P. E. Verweij, C. Viscoli, A. J. Ullmann, and E. F. I. S. Group, "Escmid* guideline for the diagnosis and management of candida diseases 2012: prevention and management of invasive infections in neonates and children caused by candida spp," *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* **18 Suppl 7**, pp. 38–52, Dec 2012.

[34] D. Andes, A. Pascual, and O. Marchetti, "Antifungal therapeutic drug monitoring: established and emerging indications," *Antimicrobial Agents and Chemotherapy* **53**, pp. 24–34, Jan 2009.

[35] W. B. Park, N. H. Kim, K. H. Kim, S. H. Lee, W. S. Nam, S. H. Yoon, K. H. Song, P. G. Choe, N. J. Kim, I. J. Jang, M. D. Oh, and K. S. Yu, "The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **55**, pp. 1080–1087, Oct 2012.

[36] S. Seyedmousavi, J. W. Mouton, P. E. Verweij, and R. J. Bruggemann, "Therapeutic drug monitoring of voriconazole and posaconazole for invasive aspergillosis," *Expert review of anti-infective therapy* **11**, pp. 931–941, Sep 2013.

[37] O. A. Cornely, M. Bassetti, T. Calandra, J. Garbino, B. J. Kullberg, O. Lortholary, W. Meersseman, M. Akova, M. C. Arendrup, S. Arikan-Akdagli, J. Bille, E. Castagnola, M. Cuenca-Estrella, J. P. Donnelly, A. H. Groll, R. Herbrecht, W. W. Hope, H. E. Jensen, C. Lass-Florl, G. Petrikkos, M. D. Richardson, E. Roilides, P. E. Verweij, C. Viscoli, A. J. Ullmann, and E. F. I. S. Group, "Escmid* guideline for the diagnosis and management of candida diseases 2012: non-neutropenic adult patients," *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* **18 Suppl 7**, pp. 19–37, Dec 2012.

[38] W. W. Hope, E. M. Billaud, J. Lestner, and D. W. Denning, "Therapeutic drug monitoring for triazoles," *Current opinion in infectious diseases* **21**, pp. 580–586, Dec 2008.

[39] K. C. van der Elst, M. van Alst, M. N. L. de Hooge, K. van Hateren, J. G. Kosterink, J. W. Alffenaar, and E. H. Scholvinck, "Clinical validation of the analysis of fluconazole in oral fluid in hospitalized children," *Antimicrobial Agents and Chemotherapy* **58**, pp. 6742–6746, Nov 2014.

[40] K. C. van der Elst, L. F. Span, K. van Hateren, K. M. Vermeulen, T. S. van der Werf, B. Greijdanus, J. G. Kosterink, D. R. Uges, and J. W. Alffenaar, "Dried blood spot analysis suitable for therapeutic drug monitoring of voriconazole, fluconazole, and posaconazole," *Antimicrobial Agents and Chemotherapy* **57**, pp. 4999–5004, Oct 2013.

[41] R. Gorodischer, P. Burtin, P. Hwang, M. Levine, and G. Koren, "Saliva versus blood sampling for therapeutic drug monitoring in children: patient and parental preferences and an economic analysis," *Therapeutic drug monitoring* **16**, pp. 437–443, Oct 1994.

[42] D. Andes and M. van Ogtrop, "Characterization and quantitation of the pharmacodynamics of fluconazole in a neutropenic murine disseminated candidiasis infection model," *Antimicrobial Agents and Chemotherapy* **43**, pp. 2116–2120, Sep 1999.

[43] D. Andes, D. J. Diekema, M. A. Pfaller, J. Bohrmuller, K. Marchillo, and A. Lepak, "In vivo comparison of the pharmacodynamic targets for echinocandin drugs against candida species," *Antimicrobial Agents and Chemotherapy* **54**, pp. 2497–2506, Jun 2010.

[44] A. Louie, G. L. Drusano, P. Banerjee, Q. F. Liu, W. Liu, P. Kaw, M. Shayegani, H. Taber, and M. H. Miller, "Pharmacodynamics of fluconazole in a murine model of systemic candidiasis," *Antimicrobial Agents and Chemotherapy* **42**, pp. 1105–1109, May 1998.

[45] M. A. Pfaller, "Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment," *The American Journal of Medicine* **125**, pp. S3–13, Jan 2012.

[46] B. D. Alexander, M. D. Johnson, C. D. Pfeiffer, C. Jimenez-Ortigosa, J. Catania, R. Booker, M. Castanheira, S. A. Messer, D. S. Perlin, and M. A. Pfaller, "Increasing echinocandin resistance in candida glabrata: clinical failure correlates with presence of fks mutations and elevated minimum inhibitory concentrations," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **56**, pp. 1724–1732, Jun 2013.

[47] D. Farmakiotis, J. J. Tarrand, and D. P. Kontoyiannis, "Drug-resistant candida glabrata infection in cancer patients," *Emerging infectious diseases* **20**, pp. 1833–1840, Nov 2014.

[48] D. Bitar, O. Lortholary, Y. L. Strat, J. Nicolau, B. Coignard, P. Tattevin, D. Che, and F. Dromer, "Population-based analysis of invasive fungal infections, france, 2001-2010," *Emerging infectious diseases* **20**, pp. 1149–1155, Jul 2014.

[49] J. W. Baddley, D. R. Andes, K. A. Marr, D. P. Kontoyiannis, B. D. Alexander, C. A. Kauffman, R. A. Oster, E. J. Anaissie, T. J. Walsh, M. G. Schuster, J. R. Wingard, T. F. Patterson, J. I. Ito, O. D. Williams, T. Chiller, and P. G. Pappas, "Factors associated with mortality in transplant patients with invasive aspergillosis," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **50**, pp. 1559–1567, Jun 15 2010.

[50] A. Burgos, T. E. Zaoutis, C. C. Dvorak, J. A. Hoffman, K. M. Knapp, J. J. Nania, P. Prasad, and W. J. Steinbach, "Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases," *Pediatrics* **121**, pp. e1286–94, May 2008.

[51] M. Bassetti, L. Taramasso, E. Nicco, M. P. Molinari, M. Mussap, and C. Viscoli, "Epidemiology, species distribution, antifungal susceptibility and outcome of nosocomial candidemia in a tertiary care hospital in italy," *PloS one* **6**(9), p. e24198, 2011.

[52] E. Castagnola, S. Cesaro, M. Giacchino, S. Livadiotti, F. Tucci, G. Zanazzo, D. Caselli, I. Caviglia, S. Parodi, R. Rondelli, P. E. Cornelli, R. Mura, N. Santoro, G. Russo, R. D. Santis, S. Buffardi, C. Viscoli, R. Haupt, and M. R. Rossi, "Fungal infections in children with cancer: a prospective, multicenter surveillance study," *The Pediatric infectious disease journal* **25**, pp. 634–639, Jul 2006.

[53] O. Gudlaugsson, S. Gillespie, K. Lee, J. V. Berg, J. Hu, S. Messer, L. Herwaldt, M. Pfaller, and D. Diekema, "Attributable mortality of nosocomial candidemia, revisited," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **37**, pp. 1172–1177, Nov 1 2003.

[54] D. L. Horn, D. Neofytos, E. J. Anaissie, J. A. Fishman, W. J. Steinbach, A. J. Olyaei, K. A. Marr, M. A. Pfaller, C. H. Chang, and K. M. Webster, "Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **48**, pp. 1695–1703, Jun 15 2009.

[55] A. Kim, D. P. Nicolau, and J. L. Kuti, "Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the united states," *Mycoses* **54**, pp. e301–12, Sep 2011.

[56] M. Mor, G. Gilad, L. Kornreich, S. Fisher, I. Yaniv, and I. Levy, "Invasive fungal infections in pediatric oncology," *Pediatric blood & cancer* **56**, pp. 1092–1097, Jul 1 2011.

[57] P. G. Pappas, J. H. Rex, J. Lee, R. J. Hamill, R. A. Larsen, W. Powderly, C. A. Kauffman, N. Hyslop, J. E. Mangino, S. Chapman, H. W. Horowitz, J. E. Edwards, W. E. Dismukes, and N. M. S. Group, "A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **37**, pp. 634–643, Sep 1 2003.

[58] L. Sung, B. J. Lange, R. B. Gerbing, T. A. Alonzo, and J. Feusner, "Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia," *Blood* **110**, pp. 3532–3539, Nov 15 2007.

[59] T. E. Zaoutis, J. Argon, J. Chu, J. A. Berlin, T. J. Walsh, and C. Feudtner, "The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the united states: a propensity analysis," *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **41**, pp. 1232–1239, Nov 1 2005.

[60] T. E. Zaoutis, K. Heydon, J. H. Chu, T. J. Walsh, and W. J. Steinbach, "Epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children in the united states, 2000," *Pediatrics* **117**, pp. e711–6, Apr 2006.

[61] A. M. Sadowska, V. Nowe, A. Janssens, E. Boeykens, W. A. D. Backer, and P. R. Germonpre, "Customizing systemic therapy in patients with advanced non-small cell lung cancer," *Therapeutic advances in medical oncology* **3**, pp. 207–218, Jul 2011.

[62] S. Seyedmousavi, J. W. Mouton, W. J. Melchers, R. J. Bruggemann, and P. E. Verweij, "The role of azoles in the management of azole-resistant aspergillosis: from the bench to the bedside," *Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy* **17**, pp. 37–50, Jul 2014.