mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Current issues in the clinical management of invasive aspergillosis – the AGIHO, DMykG, ÖGMM and PEG web-based survey and expert consensus conference 2009

M. J. G. T. Rüping,[1] J. J. Vehreschild,[1] A. Groll,[2] C. Lass-Flörl,[3] H. Ostermann,[4] M. Ruhnke[5] and O. A. Cornely[1,6,7]

[1]1st Department of Internal Medicine, University of Cologne, Cologne, Germany, [2]Infectious Diseases Research Program, Centre for Bone Marrow, Transplantation and Department of Paediatric Haematology / Oncology, Children's University Hospital, Münster, Germany, [3]Department of Hygiene, Microbiology and Social Medicine, Innsbruck Medical University, Innsbruck, Austria, [4]Medizinische Klinik III, Klinikum der Universität München-Großhadern, München, Germany, [5]Medizinische Klinik und Poliklinik II, Charité Universitätsmedizin, Campus Charité Mitte, Berlin, Germany, [6]Clinical Trials Centre Cologne, ZKS Köln, University of Cologne, Cologne, Germany and [7]Center for Integrated Oncology CIO KölnBonn, University of Cologne, Cologne, Germany

Summary

The objectives of this study were to identify unsolved issues in the management of invasive aspergillosis, identify controversies and achieve consensus. The German Speaking Mycological Society (Deutschsprachige Mykologische Gesellschaft, DMykG) invited other German infectious diseases (ID) and mycological societies to submit unsolved issues concerning the diagnosis and treatment of invasive aspergillosis. Based on these contributions, a digital web-based questionnaire of 12 questions on *Aspergillus* spp. was designed to be completed by experts of the participating societies. Controversial results were identified by a mathematical model and were discussed at a consensus conference during the 43rd Annual Meeting of the DMykG in Cologne, Germany. Forty-two individuals completed the questionnaire. Analysis showed a strong consensus on effective preventive measures, choice of antifungal agents for pre-emptive, empiric and targeted treatment, as well as the evaluation of early chest CT control scans as a measure of treatment response assessment. Opinions on the indication for a pulmonary biopsy of a halo sign in high-risk neutropenic patients and on the role of *Aspergillus* spp. PCR as well as galactomannan from serum in the assessment of treatment duration diverged in spite of discussion such that a consensus could not be reached. Using a recently published two-step approach – web-based survey plus classical panel discussion – expert consensus was achieved on 10 of 12 questions concerning the diagnosis and treatment of invasive aspergillosis.

Key words: Aspergillus, antifungal agents, diagnosis, systemic infection.

Introduction

During the last decade, major efforts have been undertaken to reduce the incidence, morbidity and mortality of invasive aspergillosis. Patients at risk include those with haematological malignancies, recipients of solid organ transplants and a heterogeneous group of other immunosuppressed patients, e.g. those under long-term corticosteroid use. Diagnostic criteria established by the European Organization for the Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) reflect the current diagnostic standard.[1] Concerning the prevention of invasive aspergillosis, several prophylactic regimens have been assessed, leading to the introduction of antifungal prophylaxis in defined high-risk

Correspondence: O. A. Cornely, MD, FIDSA, Uniklinik Köln, Kerpener Strasse 62, 50937 Köln, Germany.
Tel.: +49 221 478 6494. Fax: +49 221 478 3611.
E-mail: oliver.cornely@ctuc.de

Accepted for publication 27 September 2010

© 2011 Blackwell Verlag GmbH

doi:10.1111/j.1439-0507.2010.01989.x

groups.[2,3] Likewise, two major trials demonstrated the efficacy of voriconazole and liposomal amphotericin B for targeted first-line treatment of invasive aspergillosis.[4,5]

In spite of these advances, results from clinical trials cannot answer all questions concerning the diagnosis and treatment of invasive aspergillosis. In these situations, many physicians rely on expert opinions to guide patient management. However, identifying relevant questions and conducting expert discussions necessary for reaching a consensus usually requires considerable effort and expenditure.

The German Speaking Mycological Society (Deutschsprachige Mykologische Gesellschaft, DMykG) invited other infectious diseases and mycological societies to submit unsolved issues in the prevention, treatment and diagnosis of invasive aspergillosis. On the basis of these contributions, a digital web-based questionnaire was designed to be filled in by members of the societies involved. After analysis of the results, controversial questions were identified to be discussed at an expert consensus conference during the 43rd Annual Meeting of the DMykG in Cologne, Germany, 3–5 September 2009. The results of this discussion are given in the main body of this article.

Materials and methods

Details on survey development, survey analysis and conduction of the expert consensus conference have already been described elsewhere.[6]

Results

Participants

Ninety-eight (36.8%) of 266 invited physicians responded, and 42 (15.4%) surveys were fully completed. The following areas of speciality were most frequently identified by the participants: haematology and oncology (n = 24, 58.3%), clinical infectious diseases (n = 15; 36.6%) and microbiology (n = 10; 24.4%). Twenty-nine (70.7%) participants worked at a university hospital, nine (22.0%) in a non-university hospital and four (9.8%) in a private practice or diagnostic laboratory. Five of 12 questions concerning the diagnosis and treatment of invasive aspergillosis were answered controversially, as defined by the above criteria and therefore presented at the expert consensus conference attended by 32 survey participants.

Questions

The exact wording of the questions can be found in the appendix.

(1) Which of the following measures significantly reduce(s) the incidence of invasive aspergillosis in high-risk neutropenic patients (>10 days, <500 neutrophils)?

Background: There is considerable evidence towards a correlation between aerial fungal spore load and the incidence of invasive aspergillosis,[7] and isolation wards equipped with high efficiency particulate air (HEPA) filters have been shown to reduce the incidence of aspergillosis in a number of small trials.[8–10] Concerning the use of masks, it has been shown that disposable surgical masks do not filter small particles effectively,[11] but there is conflicting evidence concerning the efficacy of well-fitting FFP 2 and 3 masks. While these masks were shown to prevent inhalation of fungal spores,[11] data from a randomised trial in patients with haematological malignancies showed no reduction of invasive aspergillosis in the group wearing well-fitting masks, as opposed to no masks.[12]

Concerning the efficacy of antifungal prophylaxis, a controlled randomised trial in patients undergoing induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) showed a reduced incidence of invasive aspergillosis and improved survival for patients receiving antifungal prophylaxis with posaconazole 200 mg t.i.d po when compared with patients receiving itraconazole or fluconazole.[2]

Online responses: Thirty-two participants (76.2%) opted for antifungal prophylaxis, 29 (69.0%) for HEPA/LAF (high efficiency particulate air/laminar air flow) filters and 10 (23.8%) for the use of FFP 2 or 3 masks by high-risk neutropenic patients. Use of FFP 2 or 3 masks by the ward staff (n = 6; 14.3%), use of a surgical mask by the ward staff (n = 5; 11.9%) or patients (n = 4; 9.5%) and reduced exposure to pollution by construction sites (n = 3; 7.1%) were selected less frequently. Three participants (7.1%) claimed that there were no preventive measures that could significantly reduce the incidence of invasive aspergillosis. Three participants (7.1%) were not sure about the answer.

(2) In your institution, is one or more of the following strategies used in the treatment of invasive aspergillosis in neutropenic patients undergoing induction chemotherapy for AML/MDS? (pre-emptive, empiric) If yes, which antifungal is used?

Background: Pre-emptive antifungal therapy makes use of surrogate markers such as chest CT scans,[13] measurements of galactomannan in serum, bronchoalveolar

© 2011 Blackwell Verlag GmbH

lavage (BAL) fluid or cerebral spinal fluid by double-sandwich enzyme-linked immunosorbent assay (ELISA),[13,14] as well as detection of fungal nucleic acids by polymerase chain reaction (PCR)[15,16] to facilitate early treatment initiation. While the use of galactomannan has been recently included in the revised definition of invasive fungal diseases (IFD) by the EORTC/MSG,[17] pre-emptive treatment as a comprehensive approach is not recommended by current guidelines, as supportive data from controlled randomised trials are lacking.

Empiric antifungal therapy is a widely accepted standard of care in febrile neutropenic patients not responding to antibacterial broad-spectrum therapy.[18] Amphotericin B deoxycholate used to be the gold standard in this setting until non-inferiority was shown for liposomal amphotericin B and caspofungin in a series of clinical trials conducted by Walsh *et al* [19,20]. Of note, compared with liposomal amphotericin B, caspofungin was associated with fewer premature treatment discontinuations due to adverse events.[19] When randomised against liposomal amphotericin B, voriconazole failed to meet the predefined criteria for non-inferiority even though significantly less breakthrough IFD were documented ($P = 0.02$).[21] Even though the trial design might have disfavoured the voriconazole arm, it did not become a standard for empiric treatment of neutropenic fever.[22,23]

Results from the first clinical trial comparing empiric with pre-emptive treatment of IFD in 293 neutropenic patients, most of them receiving chemotherapy for AML, showed a survival rate of 97.3% in the group receiving empiric and of 95.1% in the group receiving pre-emptive treatment with amphotericin B deoxycholate (1 mg kg^{-1} day^{-1}) or liposomal amphotericin B (3 mg kg^{-1} day^{-1}). These results were consistent with non-inferiority of pre-emptive treatment. A subgroup analysis, however, failed to establish non-inferiority of pre-emptive treatment for patients receiving induction chemotherapy.[24]

Online responses: Thirty participants (71.4%) use a pre-emptive approach based on surrogate markers, e.g. *Aspergillus* spp. PCR or serum galactomannan. The distribution of antifungals used for this indication is shown in Fig. 1. Thirty-six participants (85.7%) reported to be using an empiric approach. The distribution of antifungals used for this indication is shown in Fig. 2.

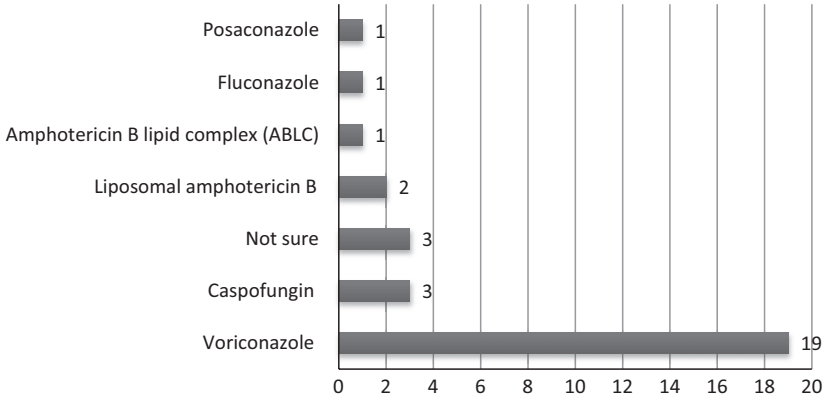

Figure 1 Distribution of antifungals used for pre-emptive treatment.

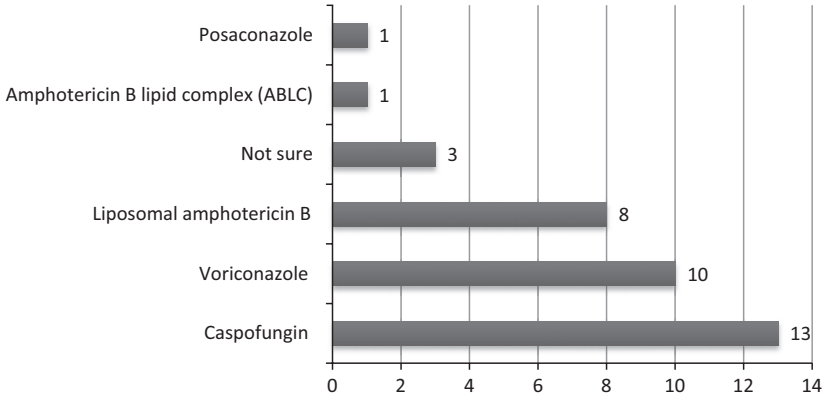

Figure 2 Distribution of antifungals used for empiric treatment.

© 2011 Blackwell Verlag GmbH

Expert discussion: After the online survey, there was no agreement concerning the choice of antifungal treatment used for the empiric approach. After discussion, a consensus was reached that caspofungin, voriconazole and liposomal amphotericin B are equally effective in this setting (n = 16; 50%). Sixteen experts (50%) abstained from voting.

(3) In a high-risk (>10 days, <500 neutrophils) patient with neutropenic fever, does the presence of a halo sign on a chest CT scan suffice to initiate antifungal treatment or should a microbiological criterion be required in addition?
Background: The revised definition of IFD by the EORTC/MSG requires the presence of a host factor, clinical features and mycological evidence for the diagnosis of a probable IFD.[17] A *post hoc* analysis of the Global Comparative Aspergillosis study conducted in neutropenic patients, however, revealed improved response to treatment and survival, if antifungal treatment was initiated in the presence of a halo sign (or air crescent sign) on chest CT, independent of mycological or histopathological confirmation.[25]

Online responses: Thirty-eight participants (90.5%) responded that they would start antifungal treatment on the basis of a halo sign. Two participants (4.8%) would prefer to have additional microbiological evidence. Two participants (4.8%) were not sure about the answer.

(4) Clinical situation: A patient with at least one host criterion according to the current EORTC/MSG guidelines presents with a halo sign on his chest CT scan. Under which circumstances should a BAL be performed?
Background: Bronchoalveolar lavage is generally considered a safe procedure, even though complications like haemorrhage or aggravation of respiratory decompensation may occur in 1–2% of all patients.[26–34] According to the current guidelines, it should be performed in patients with neutropenic fever and lung infiltrates on their chest CT scan.[35] Clearly, in severely thrombocytopenic or dyspnoeic patients, this indication may be reconsidered. Even though the use of BAL in neutropenic fever patients with chest infiltrates has been studied, it has not been reported whether the presence of this radiological sign was associated with a higher chance of isolating fungi from these BALs.[26–34]

Online responses: Thirty participants (71.4%) would always perform a BAL if the patient's clinical situation allowed for it, five (11.9%) would perform a BAL if the patient had failed first-line antifungal treatment and four (9.5%) if the halo sign had appeared under prophylactic treatment with an *Aspergillus* spp. active azole. Three participants (7.1%) would never perform a BAL in this situation and one (2.4%) if prior galactomannan or PCR tests from serum had not yielded any evidence of IFD. Three participants (7.1%) were not sure about the answer.

(5) Clinical situation: A patient with at least one host criterion according to the current EORTC/MSG guidelines presents with a halo sign on his chest CT scan. Under which circumstances would you perform a pulmonary biopsy (transbronchial, CT-guided or open) to establish the diagnosis?
Background: In neutropenic and transplanted patients with a halo or air crescent sign on chest CT, filamentous fungi were detected in 47–80% of all pulmonary biopsies. In these studies, a platelet count >50 000 μl^{-1} and coagulation values within normal limits were required for biopsy. Under these circumstances, the only life-threatening complication was a pneumothorax, which occurred in one of 137 patients (1%).[36–38]

Online responses: Eighteen participants (42.9%) would perform a biopsy if the patient had failed first-line antifungal treatment, 12 (28.6%) if a BAL and the results of prior galactomannan or PCR tests from serum had not led to a diagnosis and 10 (23.8%) if the halo sign had appeared under prophylactic treatment with an *Aspergillus* spp. active azole. Six participants (14.3%) would never perform a biopsy, while five (11.9%) would always do so if the patient's clinical situation allowed for it. Six participants (14.3%) were not sure about the answer.

Expert discussion: According to the online survey, there was no consensus on whether a pulmonary biopsy should be performed at all. After discussion, all experts agreed that a pulmonary biopsy is a useful diagnostic tool. It was also discussed whether this diagnostic procedure should remain reserved to patients failing first-line antifungal treatment. Eleven experts (34.4%) were in favour, three experts (9.4%) would not make this a prerequisite and 18 experts (56.3%) abstained from voting.

(6) For how long should an invasive aspergillosis be treated intravenously?
Background: In a landmark trial by Herbrecht *et al.*, the clinical efficacy of amphotericin B deoxycholate and voriconazole in patients with invasive aspergillosis was compared. The minimum duration of intravenous treatment in this trial was 7 days and the median duration 10 days.[5] In a trial by Cornely *et al.*, comparing different dosage regimens of liposomal

© 2011 Blackwell Verlag GmbH

amphotericin B in the treatment of invasive aspergillosis, the minimum duration of intravenous treatment was 14 days, which equalled the median treatment duration in the standard dosage group.[4] Potential associations between duration of intravenous treatment and response to treatment or overall survival were, however, not assessed in these or other publications such that the optimum duration remains unknown.

Online responses: Most participants do not adhere to a fixed minimum duration of intravenous treatment: Twenty-six (61.9%) would make their decision on a patient-to-patient basis, 16 (38.1%) would use clinical signs and symptoms to guide their decision and 10 (23.8%) would rely on chest CT scans. End of neutropenia (n = 10; 23.8%), defervescence (n = 4; 9.5%), end of all chemotherapy cycles (n = 2; 4.8%) and an overall duration of at least two (n = 2, 4.8%), three (n = 3; 7.1%) and four (n = 3; 7.1%) weeks were other choices determining intravenous treatment duration. Two participants (4.8%) were not sure about the answer.

(7) When do you usually evaluate response to treatment of invasive aspergillosis?

Background: In the above-mentioned (question 6) landmark trials on invasive aspergillosis,[4,5] response to treatment was evaluated after 12 weeks, but the choice of this point in time was based purely on clinical experience and not on evidence from comparative trials. Some authors recommend a minimum duration of 14 days of treatment before first response assessment, because unfavourable clinical development and radiological findings in this period may not be predictive of an adverse overall outcome.[39,40]

Online responses: Twelve participants (28.6%) would assess response to treatment after 1 week, eight (19.0%) after 2 weeks, one (2.4%) after 3 weeks and two (4.8%) after 3 days. Nine participants (21.4%) preferred to perform a continuous assessment. Three participants (7.1%) were not sure about the answer. Seven participants suggested other criteria for treatment assessment (n = 4 time of assessment guided by clinical status; n = 1 at least 1 week of treatment and in dependence on the neutrophil count, n = 1 after neutrophil and lymphocyte regeneration and control chest CT scan; n = 1 continuous galactomannan controls).

Expert discussion: After the online survey, there was no consensus, whether response to treatment should be assessed continuously, after 1 week or after 2 weeks. After discussion, 22 experts (68.8%) decided to assess response to treatment after 1 week, four experts (12.5%) opted for continuous assessment and none of them preferred an assessment after 2 weeks of treatment. Six experts abstained from voting.

(8) In the treatment of invasive aspergillosis, when do you perform the first chest CT scan to assess response to treatment?

Background: In major trials on the treatment of invasive aspergillosis, chest CT scans for response assessment were performed after 12 weeks of antifungal treatment.[4,5] As already discussed in question 8, the choice of this point in time was based on clinical experience and not on clinical evidence from comparative trials.

Online responses: Sixteen participants (38.1%) would perform a chest CT scan after two and 13 participants (31.0%) after 1 week of antifungal treatment. One participant (2.4%) would perform a control chest CT in less than a week. Five participants (11.9%) would like to base this decision on the clinical development of the patient and two participants (4.8%) would not perform any control chest CT scans at all, but prefer to rely solely on the patient's clinical status. Five participants (11.9%) were not sure about the answer.

Expert discussion: Based on data obtained from the online survey, the first control chest CT should be performed after 1 or 2 weeks of treatment. After discussion of the issue, 22 experts (68.8%) opted for 1 week and six (18.8%) for 2 weeks of treatment before performance of a control chest CT scan. Four experts (12.5%) abstained from voting.

(9) In the treatment of invasive pulmonary aspergillosis, how do you define treatment failure?

Background: The most commonly used assessment criteria for response to treatment were originally defined by Herbrecht *et al.* A 12-week treatment assessment included complete, response, partial response, stable disease and treatment failure. Complete response was defined as the resolution of all clinical signs and symptoms and more than 90% of the radiological lesions associated with invasive aspergillosis. Partial response was defined as clinical improvement and greater than 50% improvement in radiological findings. Stable response was defined as the absence of change from baseline or an improvement of <50%. Finally, treatment failure was defined as progression of disease.[5] Even though these definitions are still regularly used in clinical trials, their clinical applicability remains unknown.

Online responses: Progression of pulmonary infiltrates, not associated with neutrophil recovery, and

© 2011 Blackwell Verlag GmbH

progression of clinical symptoms were most frequently chosen as signs of treatment failure (n = 30, 71.4% for both), followed by rise in serum galactomannan values (n = 20; 47.6%), rise in CRP (n = 9; 21.4%), positive *Aspergillus* spp. PCR (n = 7; 16.7%) and progression of lung infiltrates, independent of neutrophil recovery (n = 3; 7.1%). Two participants (4.8%) were not sure about the answer.

Expert discussion: According to results from the online survey, there was a general agreement that the progression of clinical symptoms and radiological signs should be regarded as signs of treatment failure. It remained unclear, whether a rise in galactomannan should also be classified as such. After discussion, 17 experts (53.1%) decided that a rise in galactomannan indicated treatment failure, while three experts (9.4%) disagreed. Five experts (15.6%) abstained from voting.

(10) Do you think Aspergillus spp. PCR or galactomannan from serum should be used to assess treatment duration of invasive aspergillosis?

Background: Two moderately sized series have provided promising results concerning the use of serum galactomannan values as a tool for assessing response to treatment of invasive aspergillosis. Boutboul *et al.* monitored 37 cases of invasive aspergillosis in allogeneic transplant recipients. An increase in the galactomannan value of 1.0 over the baseline value during the first week of observation was predictive of treatment failure with a sensitivity of 44%, a specificity of 87% and a positive predictive value of 94%.[41] Similarly, Woods *et al.* detected a correlation between survival and regressing serial galactomannan in 56 patients with haematological malignancy and invasive aspergillosis.[42] Currently, there are no data on the use of fungal PCR monitoring in patients with invasive aspergillosis.

Online responses: Eighteen participants (42.9%) would use surrogate parameters for assessing the duration of treatment, while 14 (33.3%) disagreed with this statement. Ten participants (23.8%) were not sure about the answer.

(11) Which of the following antifungals is suitable for first-line treatment of invasive aspergillosis?

Background: Based on data from a randomised controlled trial, voriconazole treatment of invasive aspergillosis was successful in 52.8% and associated with a 70.8% survival rate.[5] In another randomised controlled trial, successful response to treatment with liposomal amphotericin B 3 mg kg^{-1} was 50% and survival was 72%.[4] Clinical efficacy and survival did not differ significantly between these trials. Nevertheless, because of the nephrotoxic potential of liposomal amphotericin B, voriconazole is usually recommended as first-line treatment for invasive aspergillosis with liposomal amphotericin B as an alternative, although there were no trials directly comparing both agents in this indication.[40,43] There is no clinical evidence to support the use of other antifungals as first-line treatment.

Online responses: Voriconazole was clearly preferred as first-line treatment by 38 participants (90.5%), followed by liposomal amphotericin B (n = 34, 81%), caspofungin (n = 16; 38.1%), posaconazole (n = 11; 26.2%), amphotericin B lipid complex (n = 9; 21.4%), amphotericin B deoxycholate (n = 8; 19%), micafungin n = 2; 4.8%) and anidulafungin (n = 1; 2.4%). Two participants (4.8%) were not sure about the answer.

(12) Which antifungal would you use to treat a breakthrough aspergillosis diagnosed under prophylaxis with posaconazole?

Background: Even though current guidelines recommend switch to another drug class in case of breakthrough aspergillosis under mould-active azole prophylaxis,[40,43] there are no data from clinical trials to support this recommendation.

Survey results: Liposomal amphotericin B was the agent of choice for most participants (n = 34; 81%), followed by caspofungin (n = 22; 52.4%), voriconazole (n = 7; 16.7%), amphotericin B lipid complex (n = 5; 11.9%), amphotericin B deoxycholate (n = 2; 4.8%), micafungin (n = 2; 4.8%), anidulafungin (n = 1; 2.4%) and itraconazole (n = 1; 2.4%). Three participants (7.1%) were not sure about the answer.

Conclusion

A two-step approach – web-based survey plus classical panel discussion – was used to reach a consensus on controversial issues in the diagnosis and treatment of invasive aspergillosis.[6] We invited 266 members of various infectious diseases and mycological societies to participate in an online survey on diagnosis, prophylaxis and treatment of IFD.

Five questions of 12 questions were answered controversially, as defined by predefined criteria. After an expert consensus discussion and vote, a consensus could be reached for three of these five questions. The achieved consensus on 10 questions in the treatment of invasive aspergillosis was as follows:

- Antifungal prophylaxis and HEPA/LAF filters should be used to prevent invasive aspergillosis in high-risk neutropenic patients (>10 days, <500 neutrophils).

© 2011 Blackwell Verlag GmbH

- Pre-emptive and empiric antifungal treatment are effective strategies. While voriconazole is the preferred antifungal agent in the pre-emptive setting, caspofungin, voriconazole and liposomal amphotericin B are considered equally effective in the empiric setting.
- In a high-risk patient (>10 days, <500 neutrophils) with neutropenic fever, the presence of a halo sign on a chest CT scan suffices to initiate antifungal treatment.
- A patient with at least one host criterion according to the current EORTC/MSG guidelines and a halo sign on his chest CT scan should always undergo BAL, if there is no contraindication with respect to his clinical status.
- Duration of intravenous treatment should be determined on an individual basis, as opposed to a fixed treatment duration.
- Response assessment, including a chest CT scan, should be performed after 1 week of antifungal treatment.
- Progression of pulmonary infiltrates, not associated with neutrophil recovery, progression of clinical symptoms and a rise in serum galactomannan values are considered signs of treatment failure.
- Voriconazole and liposomal amphotericin B are suitable choices for first-line treatment.
- Liposomal amphotericin B is the preferred agent of choice for the treatment of breakthrough aspergillosis occurring under mould-active azole prophylaxis.

The two questions for which no consensus could be found focused on topics with very little evidence from clinical trials:

- Indication for a pulmonary biopsy in a high-risk neutropenic patient with a halo sign on his chest CT scan.
- The role of *Aspergillus* spp. PCR or galactomannan from serum in the assessment of treatment duration.

While there is a long-standing tradition of consensus meetings on open questions concerning invasive candidiasis,[44–46] the only similar proceedings concerning the diagnosis and treatment of invasive aspergillosis were published by Segal *et al* [47]. The authors proposed a set of consensus definitions for standardisation of IFD response assessment. However, details on the consensus process were not given and the definitions were explicitly developed for the management of clinical trials, thus limiting the use of these definitions for everyday clinical practice. Our findings may serve as a point of departure for future consensus discussions on this topic.

As already stated in our previous work,[6] these meetings usually require considerable efforts and time to allow for adequate preparation and discussion. Furthermore, independent funding of consensus processes (conference centre, travel and accommodation fees) is limited. Initiation of the consensus processes with an online survey allows for timely capture of the opinions of a large and diverse group of individuals and identification of controversial issues. On-site discussion may thus be reduced to a minimum without compromising the spectrum or quality of the consensus.

Acknowledgments

OAC is supported by the German Federal Ministry of Research and Education (BMBF grant 01KN0706). MJGTR is supported by the Deutsche Forschungsgemeinschaft (DFG grant RU 1578/1-1). JJV is supported by the German Federal Ministry of Research and Education (BMBF grant 01KI0771).

Funding

All work described herein as well as the preparation of the manuscript was performed by academic researchers without external funding.

Transparency declarations

OC has received grants from Astellas Pharma, Bayer, Basilea, Genzyme, Gilead Sciences, Pfizer, Merck, Optimer, Schering-Plough, Vicuron, has worked as a consultant for Astellas Pharma, Basilea, F2G, Gilead Sciences, Pfizer, Merck, Mölnlycke Health Care, Nektar Schering-Plough, Zeneus, and served at the speakers' bureau of Schering-Plough, Astellas Pharma, Gilead Sciences, Merck, Pfizer, SpePharm and United Medical. JV has received grants from Schering-Plough and Astellas Pharma, worked as a consultant for Pfizer and Schering-Plough, and served at the speakers' bureau of Astellas Pharma, Gilead Sciences, Schering-Plough, Merck and Pfizer. MJGTR has served at the speakers' bureau of Schering-Plough, MSD, Gilead Sciences and Astellas Pharma. AG has received grants from MSD Sharp+Dohme, Gilead Sciences, Schering-Plough, worked as a consultant for Astellas, MSD Sharp+Dohme, Gilead Sciences, Schering-Plough, Cephalon, and served at the speakers' bureau of MSD Sharp+Dohme, Gilead Sciences, Schering-Plough and Pfizer. CL-F has worked as a consultant for Gilead Sciences and Pfizer and served at the speakers' bureau of Gilead Sciences, Pfizer and MSD. MR has worked as a consultant and worked at the speakers' bureau of Astellas Pharma, Gilead Sciences, Basilea, Janssen,

© 2011 Blackwell Verlag GmbH

Pfizer, MSD, Pliva and Schering-Plough/Essex and is supported by the 'Deutscher Stifterverband für die Deutsche Wissenschaft' as professor for clinical mycology in cancer patients. HO has no conflicts of interest.

References

1 De Pauw B, Walsh TJ, Donnelly JP *et al.* 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. *Clin Infect Dis* 2008; **46**: 1813–21.

2 Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.

3 Ullmann AJ, Lipton JH, Vesole DH *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; **356**: 335–47.

4 Cornely OA, Maertens J, Bresnik M *et al.* Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; **44**: 1289–97.

5 Herbrecht R, Denning DW, Patterson TF *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; **347**: 408–15.

6 Karthaus M, Rüping M, Cornely O *et al.* Current Issues in the Clinical Management of Invasive Candida Infections – The AGIHO, DMykG, ÖGMM, and PEG Web-based Survey and Expert Consensus Conference 2009. *Mycoses* 2010; (in press).

7 Alberti C, Bouakline A, Ribaud P *et al.* Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients. *J Hosp Infect* 2001; **48**: 198–206.

8 Oren I, Haddad N, Finkelstein R *et al.* Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. *Am J Hematol* 2001; **66**: 257–62.

9 Passweg JR, Rowlings PA, Atkinson KA *et al.* Influence of protective isolation on outcome of allogeneic bone marrow transplantation for leukemia. *Bone Marrow Transplant* 1998; **21**: 1231–8.

10 Sherertz RJ, Belani A, Kramer BS *et al.* Impact of air filtration on nosocomial Aspergillus infections. Unique risk of bone marrow transplant recipients. *Am J Med* 1987; **83**: 709–18.

11 Qian Y, Willeke K, Grinshpun SA *et al.* Performance of N95 respirators: filtration efficiency for airborne microbial and inert particles. *Am Ind Hyg Assoc J* 1998; **59**: 128–32.

12 Maschmeyer G, Neuburger S, Fritz L *et al.* A prospective, randomised study on the use of well-fitting masks for prevention of invasive aspergillosis in high-risk patients. *Ann Oncol* 2009; **20**: 1560–4.

13 Maertens J, Theunissen K, Verhoef G *et al.* Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis* 2005; **41**: 1242–50.

14 Maertens J, Glasmacher A, Selleslag D *et al.* Evaluation of serum sandwich enzyme-linked immunosorbent assay for circulating galactomannan during caspofungin therapy: results from the caspofungin invasive aspergillosis study. *Clin Infect Dis* 2005; **41**: e9–14.

15 Lin MT, Lu HC, Chen WL. Improving efficacy of antifungal therapy by polymerase chain reaction-based strategy among febrile patients with neutropenia and cancer. *Clin Infect Dis* 2001; **33**: 1621–7.

16 White PL, Linton CJ, Perry MD *et al.* The evolution and evaluation of a whole blood polymerase chain reaction assay for the detection of invasive aspergillosis in hematology patients in a routine clinical setting. *Clin Infect Dis* 2006; **42**: 479–86.

17 De Pauw B, Walsh TJ, Donnelly JP *et al.* 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. *Clin Infect Dis* 2008; **46**: 1813–21.

18 Klastersky J. Empirical antifungal therapy. *Int J Antimicrob Agents* 2004; **23**: 105–12.

19 Walsh TJ, Teppler H, Donowitz GR *et al.* Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med* 2004; **351**: 1391–402.

20 Walsh TJ, Finberg RW, Arndt C *et al.* Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med* 1999; **340**: 764–71.

21 Walsh TJ, Pappas P, Winston DJ *et al.* Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002; **346**: 225–34.

22 Ullmann AJ, Heussel CP, Cornely OA. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy. *N Engl J Med* 2002; **346**: 1745–7; discussion 7.

23 Marr KA. Empirical antifungal therapy – new options, new tradeoffs. *N Engl J Med* 2002; **346**: 278–80.

24 Cordonnier C, Pautas C, Maury S *et al.* Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis* 2009; **48**: 1042–51.

25 Greene RE, Schlamm HT, Oestmann JW *et al.* Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis* 2007; **44**: 373–9.

© 2011 Blackwell Verlag GmbH

26 Hummel M, Rudert S, Hof H *et al.* Diagnostic yield of bronchoscopy with bronchoalveolar lavage in febrile patients with hematologic malignancies and pulmonary infiltrates. *Ann Hematol* 2008; **87**: 291–7.

27 Rano A, Agusti C, Jimenez P *et al.* Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. *Thorax* 2001; **56**: 379–87.

28 Dunagan DP, Baker AM, Hurd DD *et al.* Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. *Chest* 1997; **111**: 135–41.

29 White P, Bonacum JT, Miller CB. Utility of fiberoptic bronchoscopy in bone marrow transplant patients. *Bone Marrow Transplant* 1997; **20**: 681–7.

30 Murray PV, O'Brien ME, Padhani AR *et al.* Use of first line bronchoalveolar lavage in the immunosuppressed oncology patient. *Bone Marrow Transplant* 2001; **27**: 967–71.

31 Hohenadel IA, Kiworr M, Genitsariotis R *et al.* Role of bronchoalveolar lavage in immunocompromised patients with pneumonia treated with a broad spectrum antibiotic and antifungal regimen. *Thorax* 2001; **56**: 115–20.

32 Hohenthal U, Itala M, Salonen J *et al.* Bronchoalveolar lavage in immunocompromised patients with haematological malignancy – value of new microbiological methods. *Eur J Haematol* 2005; **74**: 203–11.

33 Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. *Mayo Clin Proc* 2005; **80**: 1414–20.

34 Todd T, Enoch DA. Role of bronchoalveolar lavage in evaluating new pulmonary infiltrates on computed tomography in haematology patients with fever unresponsive to broad-spectrum antibiotics. *J Med Microbiol* 2009; **58**: 1660–1.

35 Maschmeyer G, Beinert T, Buchheidt D *et al.* Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: Guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. *Eur J Cancer* 2009; **45**: 2462–72.

36 Lass-Florl C, Resch G, Nachbaur D *et al.* The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. *Clin Infect Dis* 2007; **45**: e101–4.

37 Carrafiello G, Lagana D, Nosari AM *et al.* Utility of computed tomography (CT) and of fine needle aspiration biopsy (FNAB) in early diagnosis of fungal pulmonary infections. Study of infections from filamentous fungi in haematologically immunodeficient patients. *Radiol Med* 2006; **111**: 33–41.

38 Rickerts V, Mousset S, Lambrecht E *et al.* Comparison of histopathological analysis, culture, and polymerase chain reaction assays to detect invasive mold infections from biopsy specimens. *Clin Infect Dis* 2007; **44**: 1078–83.

39 Maschmeyer G, Haas A. Defining clinical failure for salvage studies. *Med Mycol* 2006; **44**: 315–8.

40 Bohme A, Ruhnke M, Buchheidt D *et al.* Treatment of invasive fungal infections in cancer patients – recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2009; **88**: 97–110.

41 Boutboul F, Alberti C, Leblanc T *et al.* Invasive aspergillosis in allogeneic stem cell transplant recipients: increasing antigenemia is associated with progressive disease. *Clin Infect Dis* 2002; **34**: 939–43.

42 Woods G, Miceli MH, Grazziutti ML *et al.* Serum Aspergillus galactomannan antigen values strongly correlate with outcome of invasive aspergillosis: a study of 56 patients with hematologic cancer. *Cancer* 2007; **110**: 830–4.

43 Walsh TJ, Anaissie EJ, Denning DW *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 327–60.

44 Edwards JE Jr, Bodey GP, Bowden RA *et al.* International Conference for the Development of a Consensus on the Management and Prevention of Severe Candidal Infections. *Clin Infect Dis* 1997; **25**: 43–59.

45 Guery BP, Arendrup MC, Auzinger G *et al.* Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part I. Epidemiology and diagnosis. *Intensive Care Med* 2009; **35**: 55–62.

46 Guery BP, Arendrup MC, Auzinger G *et al.* Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment. *Intensive Care Med* 2009; **35**: 206–14.

47 Segal BH, Herbrecht R, Stevens DA *et al.* Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. *Clin Infect Dis* 2008; **47**: 674–83.

© 2011 Blackwell Verlag GmbH

Appendix

Table A Questions and answer selections.

No.	Text	Options	Type
1	Which of the following measures significantly reduce(s) the incidence of invasive aspergillosis in high-risk neutropenic patients (>10 days, <500 neutrophils)?	Surgical mask (patient) Surgical mask (ward staff) FFP 2 or 3 mask (patient) FFP 2 or 3 mask (ward staff) HEPA/LAF (high efficiency particulate air/laminar air flow) filters Antifungal prophylaxis Other measures, please indicate None I am not sure	M
2	In your institution, is one or more of the following strategies used in the treatment of invasive aspergillosis in neutropenic patients undergoing induction chemotherapy for AML/MDS (acute myelogenous leukaemia/myelodysplastic syndrome)? If yes, which antifungal is used?	Pre-emptive treatment in the presence of positive surrogate markers (e.g. galactomannan or PCR) • We do not use this strategy • Amphotericin B deoxycholate • Amphotericin B lipid complex (ABLC) • Anidulafungin • Caspofungin • Fluconazole • Flucytosine • Itraconazole • Liposomal Amphotericin B • Micafungin • Posaconazole • Terbinafine • Voriconazole • I am not sure Empiric treatment in case of fever resistant to broad-spectrum antibiotics • We do not use this strategy • Amphotericin B deoxycholate • Amphotericin B lipid complex (ABLC) • Anidulafungin • Caspofungin • Fluconazole • Flucytosine • Itraconazole • Liposomal Amphotericin B • Micafungin • Posaconazole • Terbinafine • Voriconazole • I am not sure	M
3	In a high-risk (>10 days, <500 neutrophils) patient with neutropenic fever, does the presence of a halo sign on a chest CT scan suffice to initiate antifungal treatment or should a microbiological criterion be required in addition?	The presence of a halo suffices to initiate treatment An additional mycological criterion should be present I am not sure	S

© 2011 Blackwell Verlag GmbH

Table A (*Continued.*)

No.	Text	Options	Type
4	Clinical situation: a patient with at least one host criterion according to the current EORTC/MSG guidelines presents with a halo sign on his chest CT scan. Under which circumstances should a bronchoalveolar lavage (BAL) be performed?	Always, if the clinical condition of the patient allows it If blood tests yielded no information concerning the diagnosis If the halo sign appeared under an antifungal prophylaxis with activity against *Aspergillus* spp. If the patient did not respond to first-line antifungal treatment Never, as the cost-benefit ratio is not satisfying I am not sure	M
5	Clinical situation: a patient with at least one host criterion according to the current EORTC/MSG guidelines presents with a halo sign on his chest CT scan. Under which circumstances would you perform a pulmonary biopsy (transbronchial, CT-guided or open) to establish the diagnosis?	Always, if the clinical condition of the patient allows it If BAL and blood tests yielded no information concerning the diagnosis If the halo sign appeared under an antifungal prophylaxis with activity against *Aspergillus* spp. If the patient did not respond to first-line antifungal treatment Never, as the cost-benefit ratio is not satisfying I am not sure	M
6	For how long should an invasive aspergillosis be treated intravenously?	In dependence on chest CT control scans Until defervescence Until conclusion of all chemotherapy regimens At least until recovery from neutropenia For at least 2 weeks For at least 3 weeks For at least 4 weeks In dependence on clinical improvement Individual decision I am not sure	M
7	When do you usually evaluate response to treatment of invasive aspergillosis?	After <1 week After 1 week After 2 weeks After 3 weeks Not at all. I rely on the clinical picture. Other, please indicate: I am not sure	S
8	In the treatment of invasive aspergillosis, when do you perform the first chest CT scan to assess response to treatment?	No 3 days 1 week 2 weeks 4 weeks 8 weeks Other duration, please indicate	S
9	In the treatment of invasive pulmonary aspergil losis, how do you define treatment failure?	Progression of pulmonary infiltrates under therapy Progression of pulmonary infiltrates under therapy, if not associated with neutrophil recovery Progression of clinical symptoms Rise in CRP under therapy Rise of galactomannan in serum Positive *Aspergillus* spp. PCR under therapy Other, please indicate: I am not sure	M
10	Do you think *Aspergillus* spp. PCR or galactomannan from serum should be used to assess treatment duration of invasive aspergil losis?	No Yes I am not sure	S

© 2011 Blackwell Verlag GmbH

Table A (*Continued.*)

No.	Text	Options	Type
11	Which of the following antifungals is suitable for first-line treatment of invasive aspergillosis?	Amphotericin B deoxycholate Amphotericin B lipid complex (ABLC) Anidulafungin Caspofungin Fluconazole Itraconazole Liposomal Amphotericin B Micafungin Posaconazole Voriconazole Other, please indicate: I am not sure	M
12	Which antifungal would you use to treat a breakthrough aspergillosis diagnosed under prophylaxis with poscaonazole?	Amphotericin B deoxycholate Amphotericin B lipid complex (ABLC) Anidulafungin Caspofungin Fluconazole Itraconazole Liposomal Amphotericin B Micafungin Voriconazole Other, please indicate: I am not sure	M

S, one choice only; M, multiple selections possible.

© 2011 Blackwell Verlag GmbH