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Three major achievements of the Infections Disease Group

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ABSTRACT

The EORTC Infectious Disease Group (IDG) and its forerunners, the International Antimicrobial Therapy Cooperative Group (IATCG) and the Invasive Fungal Infection Group (IFIG), have helped drive and develop clinical practice in the management of bacterial and fungal infectious diseases. Besides undertaking seminal studies, the group in its various forms has played a key role in understanding the nature and management of the infectious complications that arise during the treatment of cancer, particularly hematological malignancies. The IATCG was also instrumental in setting the stage for large randomized controlled trials to address therapies for dealing with infections that developed during neutropenia. The three most important achievements of the group were in finding a rational basis for managing bacterial and fungal infections, the establishment of disease definitions, and the development of the guidelines.

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1. Introduction

The EORTC Infectious Disease Group (IDG) and its forerunners, the International Antimicrobial Therapy Cooperative Group (IATCG) and the Invasive Fungal Infection Group (IFIG), have helped drive and develop clinical practice in the management of bacterial and fungal infectious diseases. Besides undertaking seminal studies, the group in its various forms has played a key role in understanding the nature and management of the

infectious complications that arise during the treatment of cancer, particularly hematological malignancies. The IATCG was also instrumental in setting the stage for large randomized controlled trials to address therapies for dealing with infections that developed during neutropenia.

The IATCG activities started in 1973; a landmark study was published in 1978 that involved 625 patients and showed that infections due to Gram-negative bacteria could be managed best with a beta-lactam antibiotic and an aminoglycoside. The study demonstrated that continuing the aminoglycoside was not always necessary, thereby reducing the risk of toxicity. The group also succeeded in joining forces first with the National Cancer Institute of Canada-Clinical Trials Group and later on

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Table 1 – Response rates in granulocytopenic patients with cancer who were treated with antibiotics for microbiologically documented infections¹

| Pathogen | Carbenicillin plus cephalothin ^a | Carbenicillin plus gentamicin ^a | Gentamicin plus cephalothin | Total |
|-------------------------------|---|--|-----------------------------|--------------|
| <i>Pseudomonas aeruginosa</i> | 4/8 (50) | 10/16 (63) | 5/13 (38) | 19/37 (51) |
| <i>Klebsiella</i> species | 9/15 (60) | 12/22 (55) | 6/17(35) | 27/54 (50) |
| <i>Escherichia coli</i> | 8/18 (44) | 22/30 (73) | 18/27 (67) | 48/75 (64) |
| Other Gram-negative bacilli | 4/9 (44) | 8/15 (53) | 4/7 (57) | 16/31 (52) |
| Total Gram-negative bacilli | 25/50 (50) | 52/83 (63) | 33/64 (52) | 110/197 (56) |
| <i>Staphylococcus aureus</i> | 18/22 (82) | 12/13 (92) | 13/19 (68) | 43/54 (80) |
| Other Gram-positive cocci | 5/11 (46) | 5/8 (63) | 7/11 (64) | 17/30 (57) |
| Total Gram-positive cocci | 23/33 (70) | 17/21 (81) | 20/30 (67) | 60/84 (71) |
| Other bacteria | 1/2 | 2/3 | 6/8 | 9/13 |
| Total of all pathogens | 49/85 (58) | 71/107 (66) | 59/102 (58) | 179/294 (61) |

Data are number of patients with response/number tested (percentage). Some patients were infected with multiple pathogens.
^a Ticarcillin was used instead of carbenicillin in approximately one-third of the cases.

with the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto Infection Program (GIMEMA). The IATCG became renowned throughout the scientific community and also helped establish a clear link between supportive care and the EORTC.

The IFIG was founded in 1992. In a similar vein as the IATCG, the IFIG completed another landmark study that established the standard of care for treating invasive aspergillosis, a disease that grew in prominence due, in part, to the success in managing bacterial infections. This study also helped forge a link with the Mycosis Study Group (MSG) of the USA which proved fruitful in the development of consistent definitions of the invasive fungal disease and in devising response criteria to therapy that have been adopted by journals, regulatory authorities and the scientific community as a whole.

In 2005, the IATCG and the IFIG were merged in a unique group aimed at studying all types of infectious complications in cancer patients, the IDG. Last but not least, the IDG has been an active partner of the European Leukaemia Network, the European Group for Blood and Marrow Transplantation, and the International Immunocompromised Host Society in producing the European Conference on Infections in Leukemia (ECIL) guidelines for managing viral, bacterial, and fungal diseases. The ECIL has convened every two years since 2005 with the next meeting planned for 2013. The three most important achievements of the group in the field of managing bacterial and fungal infections, establishment of disease definitions, and the development of the guidelines are summarized below.

2. Achievements in bacterial infections

In the 1970's, managing infections arising from neutropenia was challenging and, though there were many antimicrobial drugs available and the most common

causes of bacterial infection were known, there was no standard of care. It was already known that mortality due to Gram-negative bacterial infections could best be reduced by starting therapy empirically as soon as a neutropenic patient became febrile.¹ Formed in 1973, the IATCG initiated a study of three different antimicrobial regimens for patients with cancer or aplastic anemia, who were granulocytopenic and who had developed fever that had no obvious non-infective cause.²

The aims of the study were three-fold: (1) to define the types of infection that occur, (2) to evaluate predisposing factors, and (3) to compare the efficacy and toxicity of three commonly utilized empirical antibiotic combinations, one a so-called double beta-lactam regimen, carbenicillin or ticarcillin plus cephalothin, and two different beta-lactam-aminoglycoside regimens, namely, carbenicillin or ticarcillin plus gentamicin, and cephalothin plus gentamicin (Table 1). Besides showing that a combination of carbenicillin (or ticarcillin) and an aminoglycoside achieved higher response rates, the study noted that almost 1 in 5 fevers were probably not due to infection and another 1 in 5 could only be considered possibly due to infection. However, since at the onset of fever there was no way of distinguishing between these fevers and those due to clinically defined or microbiologically defined infections, patients should be treated promptly at the onset of fever to reduce mortality due to infections caused by Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*.¹

The next IATCG study compared ceftazidime combined with a short or long course of amikacin for empirical therapy and confirmed that a short course of an aminoglycoside was as effective and less toxic than a conventional long course of the combination for the empirical therapy of Gram-negative bacteremia of patients with cancer and granulocytopenia.³ Another controversial issue at that time was whether or not

vancomycin should be included as part of the empirical regimen.⁴ As there were no differences in outcome between patients with bacteremia due to Gram-positive cocci and those without it was concluded that including vancomycin in the initial empirical antibiotic regimen was not necessary.

The availability of the broad-spectrum beta-lactam antibiotics piperacillin and meropenem allowed the group to explore their effectiveness as empirical therapy either in combination with amikacin⁵ or alone.⁶ Hence, through their efforts the IATCG provided four regimens that were effective for treating patients who were granulocytopenic and who had developed fever that had no obvious infective cause.

The next study was undertaken to see whether or not an oral regimen of oral ciprofloxacin plus amoxicillin-clavulanate would offer advantages such as improved quality of life and lower cost over an intravenous regimen of ceftriaxone plus amikacin.⁷ As equivalence was demonstrated during a planned interim analysis, the trial was terminated early. Hence, low-risk patients with cancer who had fever and granulocytopenia could be given oral therapy and might be able to be managed further as outpatients.

The group then revisited the issue of coverage for infections due to Gram-positive cocci and embarked on a prospective, double-blind trial to see whether the addition of a glycopeptide reduced the time to defervescence in neutropenic patients with cancer who had persistent fever 48–60 h after the initiation of empirical piperacillin/tazobactam therapy.⁸ As there was no measurable benefit to these patients, the practice of routinely adding vancomycin for persistent fever was to be discouraged. This had important implications, given the increase in vancomycin-resistant enterococci associated with a broad empirical use of vancomycin.

3. Achievements in fungal infections

The IATCG also explored the need for empirical antifungal therapy. There were six documented fungal infections in 64 (9%) with four deaths in patients randomized to not receive the antifungal therapy, compared with only one fungemia and no deaths among the 68 patients (1%) treated empirically with amphotericin B. Although there was no statistically significant difference in survival between the two groups, those patients who had not received any antifungal prophylaxis appeared to benefit from empirical antifungal therapy.

The newly formed IFIG conducted a prospective, multicentre surveillance of candidaemia among patients being treated for cancer.⁹ *Candida albicans* was responsible for most infections involving patients with solid tumors, but in only 1 out of 3 cases with hematological malignancies. Neutropenia in solid tumor patients and

acute leukemia, and antifungal prophylaxis in patients with hematological malignancies were significantly associated with candidemia due to other *Candida* species. Mortality was associated with older age, severity of the underlying disease, fungemia due to *C. krusei* and *C. glabrata*, allogeneic bone marrow transplantation, septic shock, and the lack of antifungal prophylaxis.

The group then initiated and completed the landmark trial of voriconazole versus amphotericin B deoxycholate for the primary therapy of invasive aspergillosis.¹⁰ There were 144 patients in the voriconazole group and 133 patients in the amphotericin B deoxycholate group with either definite or probable aspergillosis, and the majority had had an allogeneic hematopoietic-cell transplant or were treated for acute leukemia or other hematological malignancies. At week 12 successful outcomes were seen in 1 out of 2 patients given voriconazole and 1 out of 3 given amphotericin B deoxycholate. Seven out of 10 in the voriconazole group survived as did 6 out of 10 in the amphotericin B deoxycholate group, but the latter group experienced more severe drug-related adverse events (Fig. 1). Consequently, voriconazole became the drug of choice for treating invasive aspergillosis given the better responses, improved survival, and fewer severe side effects. Based on results from this study voriconazole became the benchmark for other drugs to establish efficacy for treating invasive aspergillosis, and it is regarded as first-line treatment in all guidelines published thus far. The study itself confirmed that randomized clinical trials remain the single best instrument for testing drugs for preventing and treating invasive fungal diseases. The data generated also provided important information on the role of imaging¹¹ and helped to establish an evidence base for the revised definitions of invasive fungal diseases that were published in 2008.¹²

4. Major initiatives for worldwide education and development of guidelines

The IDG has substantially contributed to the development of treatment guidelines as well as the worldwide education, including the web-based education. Clarity and uniformity in defining infections and providing guidance for their treatment are important factors both in the management of patients, as well as in clinical research, as standardized definitions strengthen the consistency and reproducibility of the results. The most important initiatives of the IDG are the definitions of diagnosis for fungal diseases and their treatment and the development of ECIL guidelines, as discussed below in more detail.

4.1. Definitions of invasive fungal diseases

The definitions for diagnosis of invasive fungal disease have been developed in collaboration with the Mycosis Study Group (MSG). The definitions were originally

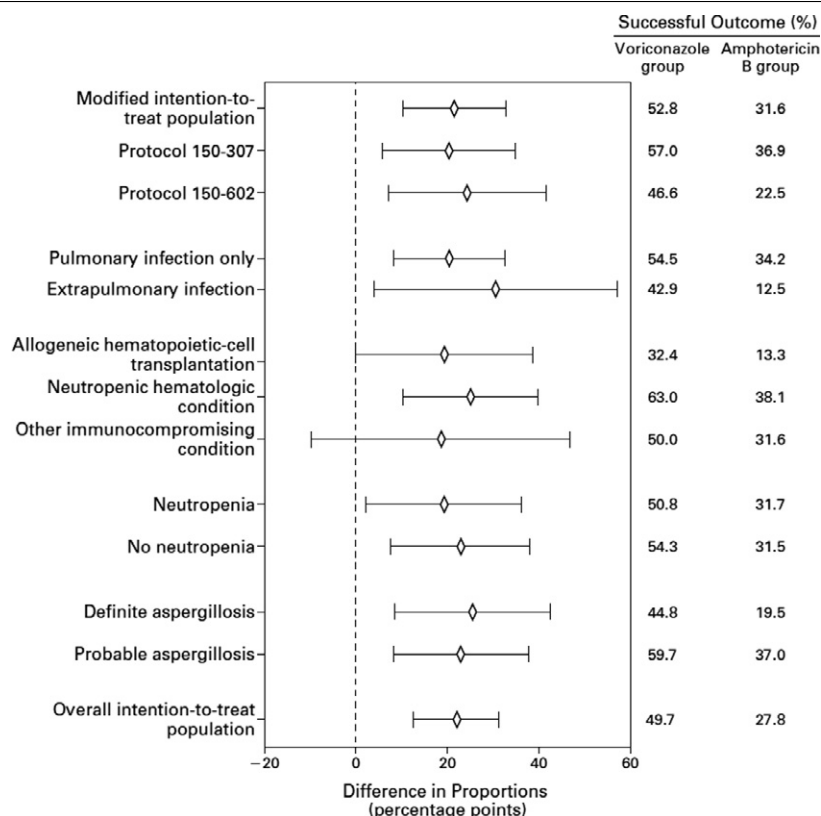


Fig. 1 – Response rates in the modified intention-to-treat population according to the study protocol, site of infection, underlying condition, neutropenic status, degree of certainty of the diagnosis, and in the intention-to-treat population. Results are expressed as the difference (with 95% confidence intervals) between the voriconazole group and the amphotericin B deoxycholate group in the rate of successful outcomes.¹⁰

published in 2002¹³ and the revised version in 2008.¹² The definitions classify the fungal diseases as “proven,” “probable,” and “possible” invasive fungal disease. The category of “proven” invasive fungal disease can apply to any patient, regardless of whether the patient is immunocompromised, whereas the “probable” and “possible” categories are proposed for immunocompromised patients only. These revised definitions of invasive fungal disease are intended to advance clinical and epidemiological research, and may serve as a useful model for defining other infections in high-risk patients.¹²⁻¹⁴ They have also been adopted by the Committee for Medicinal Products for Human Use (CHMP) in its “Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease”.¹⁵

4.2. Definitions for response to antifungal therapy

Defining the response to antifungal therapy has been challenging – not least due to the inconsistencies in previous criteria. Hence definitions for response to the treatment of invasive fungal disease were developed again in collaboration with the Mycosis Study Group. These definitions have also been adopted in the “Guideline on the clinical evaluation of antifungal agents

for the treatment and prophylaxis of invasive fungal disease”.¹⁶

4.3. European Conference on Infections in Leukaemia (ECIL) guidelines

In 2005, several groups including the European Group for Blood and Marrow Transplantation, the IDG from the European Organization for Treatment and Research of Cancer, the European Leukaemia Net and the Immunocompromised Host Society created the European Conference on Infections in Leukaemia (ECIL). The main goal of ECIL is to elaborate guidelines or recommendations for the management of infections in leukemia and stem cell transplant patients. EORTC IDG has been the key contributor in the development in these guidelines. The ECIL guidelines have been published as three separate sets of publications, ECIL-1 held in 2005,¹⁷⁻²⁴ ECIL-2 held in 2007,^{25,26} and ECIL-3 held in 2009.²⁷⁻³⁰ The proceedings of the ECIL-4 conference held in 2011 will be submitted for publication in 2012.

5. The future of the Infectious Disease Group

At present the group is actively pursuing a large clinical Phase III strategy study in more than 550 patients.

This study is expected to increase cross-fertilization between the different EORTC disease-oriented groups and enhance future collaboration with other groups with similar aims and objectives. Collaboration in clinical research and practice is of paramount importance today, as the management of infectious complications in cancer patients is becoming increasingly more complex. Future challenges include the initiation and completion of relevant studies not only to attract young investigators into the field but also to consolidate what we have learned and keep ahead of the new challenges that face us.

The field of infectious diseases is in a constant state of flux. At present there is a greater understanding of the role of chemotherapy-induced damage of the mucosa (mucosal barrier injury) in infection, an appreciation of the increase in antimicrobial resistance, continuous changes in the nature of and extent of compromised immunity related to new ways of treating cancer, and the increasing number of patients being treated for cancer as the population ages. At the same time there are more diagnostic opportunities that include imaging and molecular techniques. However, the choice of antimicrobial agents has become more difficult due to emergent resistance, drug interactions and adverse effects. Moreover, there are fewer drugs in the pipeline making it imperative that we learn to use what we have optimally and sparingly. Funding of health care also remains an issue as we struggle to provide optimal care while minimizing costs. This necessitates adoption of strategies for use and the creation of care pathways to make the best use of the diagnostic tools and drugs we have available. The IDG will also maintain a strong focus on the educational activities and will continue hosting joint sessions at international conferences in its own fields. The group will continue to focus on highly relevant clinical and translational research activities, as well as on quality educational projects that meet the general interests of investigators in the field of infectious complications affecting patients with cancer.

6. Conflict of interest statement

Liisa Pylkkanen and Marianne Paesmans declare no conflicts of interest. J Peter Donnelly consulted for and received honoraria and research funds from Gilead and Pfizer, consulted for Astellas, and received research funds from MSD. Catherine Cordonnier consulted for and received honoraria, research funds and travel reimbursements from Pfizer, MSD. Matteo Bassetti consulted for Gilead Sciences, Merck Sharp and Dohme, Novartis, Pfizer and Schering Plough, and has been paid for talks on behalf of Angelini, Astellas, Astra Zeneca, Aventis, Bayer, Cephalon, Glaxo SmithKline, Gilead Sciences, Jansen Cilag, Merck Sharp and Dohme, Novartis, and Pfizer.

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