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Update on community respiratory viral infections

Edited by Per Ljungman, MD, PhD

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During the past decade, there has been great interest in community respiratory viral infections in hematopoietic stem cell transplant (HSCT) recipients, but many questions remain about when to intervene and how to manage these patients. Before clinicians can consider management, they must first appreciate the epidemiology of these infections and the importance of early diagnosis. These and related issues were addressed at a CME symposium, *Community Respiratory Viral Infections in the BMT Population: Update on Prevention and Management*, chaired by Dr. Per Ljungman and held on February 15, 2001, during the Tandem BMT Meetings of the IBMTR/ABMTR and the American Society for Blood and Marrow Transplantation (ASBMT) at Keystone Resort, Colorado.

Epidemiology and diagnosis

Physicians involved in HSCT now recognize that respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, and possibly even rhinoviruses cause morbidity and mortality among their hospitalized patients. The acute respiratory infections caused by such viruses all present similarly, observed Dr. Janet A. Englund of the University of Chicago Pritzker School of Medicine. "A patient with any of these respiratory viruses may present with a common cold, a stuffy nose, upper respiratory tract disease, pharyngitis, laryngitis, tracheobronchitis, flu syndrome, bronchiolitis, or pneumonia," she noted. "Although during peak epidemic months it may be easy to conclude which virus is responsible, immunocompromised HSCT recipients are not typical of the population at large, and community respiratory virus seasons last much longer for them than for healthy persons."

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The perfect time to be in Florida – 2002 Tandem BMT Meetings –

February 22–26 at Coronado Springs Resort in Orlando
by D'Etta Waldoch, CMP

The increasingly popular Tandem BMT Meetings – two comprehensive scientific meetings focusing on issues in blood and marrow transplantation and held back-to-back each year – will be held next year at the beautiful Coronado Springs Resort in Orlando, Florida, February 22–26. And February is *the perfect time* to be in Florida!

The Annual Participants' Meeting of the IBMTR/ABMTR, February 22–24, will immediately precede the Annual Meeting of the American Society for Blood and Marrow Transplantation (ASBMT) February 24–26.

The two conferences, held last winter at Keystone Resort in the Colorado Rockies, offer complementary scientific programs that address the latest developments in BMT patient care, clinical research and laboratory research. More than 1300 blood and

marrow transplant investigators, clinicians, nurses, pharmacists and support personnel attend the Tandem BMT Meetings annually.

The spacious Coronado Springs Convention Center provides an ideal setting for plenary sessions on stem cell plasticity, immunopharmacology, myeloma, thymic reconstitution and cellular immunotherapy. Concurrent sessions will investigate transplant-related topics such as solid tumors, mesenchymal stem cells, apoptosis, quality of life, biologic modification in vivo and in vitro, statistical methods, pediatric malignancies, allo antigens for hematologic tumor specific immunotherapy, mini-transplants and late effects. Topics for the 2002 scientific workshops include stem cell expansion, managing infections, GVHD, ethics, gene therapy,

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Perspectives



John M. Goldman, DM

Immediate Past-Chair, IBMTR Advisory Committee, Professor and Chairman, Department of Haematology, Imperial College School of Medicine / Hammersmith Hospital, London, UK

Hematopoietic stem cell transplantation – the past and now the future

“Old men forget ...”¹ but they can reminisce well and sometimes they see the general picture with a clearer perspective than their younger colleagues. The problems of bone marrow transplantation twenty years ago are still fairly prominent in my mind. Stem cell biology and kinetics were poorly understood, we knew little about stem cell “homing” or hematopoietic growth factors, we did not really know if transplantation could cure leukemia, we knew little of the mechanisms underlying GVHD or how to prevent it, opportunistic infections were poorly defined – to name only a few of the challenges. Twenty years later, major advances have been made. Survival post-transplant has improved considerably and we know that many patients are indeed cured by allogeneic stem cell transplantation. We understand more about the pathogenesis of GVL and GVHD, we have defined the use of blood-derived SCT to a large extent, and we are now in the era of “reduced intensity conditioning” SCT – to name just a few of the significant advances. Most remarkable is the spread of transplant technology to specialist centers in every developed country in the world. Equally remarkable is the fact that most centers in most countries report clinical information to the

International Bone Marrow Transplant Registry, which as a consequence is able to analyze transplant outcome in a wide variety of clinical situations and thus to publish scientific papers on almost every aspect of hematopoietic SCT – papers that have major credibility and are accepted worldwide as standards by which other scientific work can be judged. IBMTR’s success is a reflection of astute strategic planning by those who led the organization in the early days and of continuing high standards of planning and meticulous implementation by those who lead the enterprise today – aided of course by a totally committed team in Milwaukee.

What now of the future of clinical transplantation? Indications for transplant have always been changing, and the recent introduction of imatinib mesylate (formerly ST1571) for treatment of chronic myeloid leukemia is a cogent reminder that transplant technologies must at all times be viewed in comparison with the best available alternative treatments. Imatinib mesylate induces hematological control in nearly 100% of CML chronic phase patients and major cytogenetic responses in more than 50% of cases. It is relatively free of toxicity, at least in comparison with interferon-alfa. Does it produce molecular remissions? Does it prolong life? Does it cure CML patients? We do not have these answers. Some have predicted that it will eliminate the

need for transplant for CML patients. This does not (yet) appear to be the case. Indeed it is possible that permanent eradication of CML will depend always on a GVL effect. If so, imatinib mesylate will prove an important adjunct but no panacea in the management of CML. Thus far, the STI/imatinib story serves mainly to illustrate the increasing complexity of decision making in the treatment of leukemia. It does not in any sense suggest the obsolescence of stem cell transplant technology.

Indeed the demonstration in very recent years that stem cells are far less lineage restricted than was previously thought to be the case now suggests the possibility of very much wider use of allogeneic or autologous SCT technology. If, for example, stem cells derived from the bone marrow do really have the capacity to regenerate cardiac or hepatic tissues, if muscle-derived stem cells can reconstitute hematopoiesis, as seems to be the case in murine models, then clearly stem cell usage is only in its infancy. If these experimental results can translate to clinical practice, the number of diseases that could yield to SCT is enormous. The recognition of this stem cell “plasticity” may in the near future be seen as one of the most significant advances of the early years of the 21st century. In terms of data collection and analysis, the IBMTR still has much to do.

1. Shakespeare W. *Henry V.*

Perspectives



Alexandra H. Filipovich, MD

*IBMTR Advisory Committee Chair
Children's Hospital Medical Center, Cincinnati, Ohio*

It is a great privilege for me to join the leadership team at the IBMTR Statistical Center in Milwaukee and my professional colleagues from more than 350 participating institutions in continuing the critically important examination of multi-institutional results of hematopoietic transplants and defining future goals of clinical research in our field. The past year saw the publication of 17 peer-reviewed studies and reviews, with an additional ten in press and six under review, as well as more than 50 presentations at national and international meetings of outcomes research emerging from the IBMTR database. Scientific partnerships between the IBMTR and the European Group for Blood and Marrow Transplantation and the National Marrow Donor Program have expanded and strengthened with a number of ongoing collaborative analyses. These include comparisons of treatment outcomes by donor and graft types, projects that could not be done without such cooperation. Changing practices in the field, such as use of hematopoietic stem cell transplantation for "new indications", e.g. autoimmune disorders, allotransplants for solid tumors, or application of transplantation in new ways, e.g. in utero transplantation and gene transfer, challenge a voluntary registry with choices about whether and how to efficiently monitor the efficacy of such interventions.

Some of the exciting opportunities to be considered by our organization include: (1) the development of new approaches to prospective study design; and (2) the collection and integration of molecular data with retrospective and prospective analyses of clinical outcomes.

Unprecedented accomplishments in biomedical bench research, including publication of the human genome sequence and demonstration of the feasibility of immune response profiling with genomic microarrays, challenge the IBMTR to refine new research strategies. While the IBMTR has undertaken measures to curb the amounts of clinical data collected on patients, collection of detailed laboratory information on selected topics and in selected patients will likely be necessary to understand the interplay between genetics and results of clinical interventions.

For those of us daily "in the field", many of the pivotal questions in clinical transplantation practice still await answers. A partial list of topics that we, as clinical investigators, wish to better understand includes the following:

1. *Donor and stem cell source selection:* Does the "best product" vary by underlying disease or recipient characteristics (e.g. cell dose requirements) and/or preparative regimen? Retrospective analyses and prospective randomized trials based on evaluable retrospective data can help answer these questions.
2. *Impact of full vs. mixed chimerism:* What factors govern stable mixed chimerism and its relationship to correction or control of different underlying disease processes? Does mixed chimerism affect graft durability? New study designs and additional data collection will be needed to study these questions.
3. *The quest for the safest and most reliable conditioning / GVHD prophylaxis regimens:* Disease,

recipient and graft type specific issues are being studied by the IBMTR and collaborating registries, but prospective randomized trials should be undertaken when promising alternatives are identified and patient numbers permit.

4. *Late effects of underlying disease and survival after transplantation:* Data on late complications of immune dysregulation, physical and psychological sequelae, and consequences of surviving previously lethal genetic defects are still sparse. Follow-up studies of long-term survivors and design of future studies to consider these endpoints should be emphasized.
5. *Prevention of posttransplant relapse of malignant diseases:* How can we measure the relative contributions of preparative therapies vs. different immunotherapies pre and posttransplant? Thought must be given to required data collection in prospective trials.
6. *Immune reconstitution:* The contributions of donor and recipient characteristics and methods of GVHD prevention and treatment to delayed immune recovery require more examination, since infections remain the major cause of mortality, especially in alternative donor transplants. Retrospective analyses have only a limited role to play in this important area; recovery of immunity should be a major focus in future.

I look forward to working with the membership of the IBMTR to explore the opportunities and address obstacles in our pursuit of better therapies for our patients.

Update on community respiratory viral infections – continued from page 1

Dr. Englund cited three other differences between immunocompromised hosts and healthy persons with respect to the acquisition and clinical course of community respiratory viral infections. First, infections persist much longer in immunocompromised hosts than in otherwise healthy people. "Patients can shed viruses for prolonged periods of time, up to months," Dr. Englund said. Although viral concentrations are low, the virus persists and, patients remain contagious. Second, the rate of nosocomial infection is much higher among immunocompromised hosts. Nosocomial infections may be acquired directly from hospital staff, from visitors, or from other patients, with staff

members potentially serving as intermediaries. Finally, pneumonia and death due to community respiratory viruses occur more frequently in immunocompromised hosts. RSV causes the greatest morbidity and mortality, with overall mortality rates of 30% to 40%. Among patients with RSV pneumonia, some studies report mortality rates as high as 80%. The highest frequency of progression to fatal viral pneumonia is reported for RSV infections in recently transplanted HSCT recipients and myelosuppressed patients with leukemia. In contrast, overall mortality ranges from 10% to 15% for influenza virus infection and is less than 20% for parainfluenza

virus infection. Upper respiratory symptoms of community respiratory viral infections typically precede involvement of the lower respiratory tract. Confirmatory tests are necessary to identify the pathogen. Serologic tests are useless, and viral culture takes too long, although the latter remains the gold standard. "Rapid detection is the way to go," Dr. Englund noted. The importance of a good specimen, obtained from a nasopharyngeal aspirate, deep nasopharyngeal swab, or nasal wash, cannot be overemphasized; a superficial nasal swab or throat swab will miss most RSV infections. "You should not delegate obtaining a culture to the least educated

The perfect time to be in Florida 2002 – Tandem BMT meetings – continued from page 1

DLI, cord blood transplants, autoimmune diseases, relapse, haploidentical transplants, and immune deficiencies.

The Tandem BMT Meetings in Orlando will also include IBMTR/ABMTR and ASBMT committee meetings, poster sessions, satellite programs and exhibits, a Doctor's Job Fair and concurrent conferences for ONS nurses, clinical research coordinators, BMT pharmacists and transplant center administrators and directors.

Co-chairs for the IBMTR/ABMTR Annual Participants' Meeting are *John Goldman, DM*, Imperial College of Medicine / Hammersmith Hospital, London, and *Armand Keating, MD*, University of Toronto / Princess Margaret Hospital, Ontario. The program chair for the ASBMT Annual Meeting is *Ronald Gress, MD*, National Institutes of Health, Bethesda, Maryland.

Distinctive southwestern architecture marks the Coronado Springs Resort. Located in the heart of the Walt Disney World Resort in Lake Buena Vista, the Resort offers 1,967 guest rooms and suites well-equipped for business travel in three distinct villages: the Casitas, Rachos and Cabanas. Attention to detail abounds in creative landscaping with impressive lake views and an enticing selection of recreational amenities and services for relaxation during free time. Coronado Springs is adjacent to Epcot, MGM Studios and Disney's Animal Kingdom, but away from the roar of the crowd. Coronado Springs offers state-of-the-art meeting and convention facilities and a business center to keep conference attendees connected to home.

For updates about the 2002 meetings, housing and transportation to Orlando, keep an eye on the IBMTR/ABMTR web site: www.ibmtr.org.

But we can't ski in Orlando!!!

- Animal Kingdom Theme Park
- Babysitting and Children's Activities Centers
- Backstage tours
- Bongos Cuban Café
- Championship golf courses
- Disney Institute hands-on programs
- Disney MGM Studios
- DisneyQuest interactive adventures
- Downtown Disney's all-day, all-night playground for adults
- Epcot Center
- Fantasia Gardens
- Fireworks
- Fishing excursions
- Full-service health clubs and spas
- House of Blues
- Jogging trails
- Magic Kingdom Park
- Marinas and watercraft rentals including mini power boats, canopy boats, pontoon boats, jet boats, sailboats, catamarans, canoes and pedal boats
- Miniature golf
- Movies
- Pleasure Island's live stage shows, sensational nightclubs, country, rock & roll, jazz and live comedy

Right!...

- Regional cuisine featuring everything from elegant, upscale and unique dinner shows to quick and casual in seafood, steaks and chops and vegetarian: British, Californian, Chinese, Creole, Cajun, Cuban, French, German, Italian, Japanese, Mediterranean, Mexican, Moroccan, Norwegian, Nuevo Latino, Pacific Northwest & Polynesian.
- Shopping for character merchandise and sundries; men's, women's and children's finer apparel; sports apparel & vacation wear; crafts, collectibles and fine treasures; specialty items
- Surfing program
- Swimming
- Tennis
- Water Parks: Blizzard Beach, River Country and Typhoon Lagoon
- Waterskiing, wakeboarding and parasailing
- Wildhorse Saloon
- Winter Summerland
- Wolfgang Puck

And so much more...

Update on community respiratory viral infections – continued from page 4

and least motivated person on your hospital team,” Dr. Englund advised, “which is what sometimes happens.”

At the M. D. Anderson Cancer Center in Houston, viral screening of patients before transplantation and meticulous protective measures to reduce the risk of nosocomial transmission – uniform use of masks, hand washing, and gloves; restriction of visitors; avoidance of crowded areas; and isolation and treatment of patients with respiratory infections – have substantially reduced the incidence of community respiratory viral infections among hospitalized HSCT recipients during the fall and winter months. At the Fred Hutchinson Cancer Research Center in Seattle, all patients with symptoms of a respiratory viral infection undergo a deep nasopharyngeal swab and nasal wash, according to Dr. W. Garrett Nichols. “We do antigen detection by DFAs [direct fluorescent antibodies], shell vial culture, and conventional culture on these patients and on all BAL [bronchoalveolar lavage] fluid,” he said, “regardless of whether the patient presents with only a nodule [on chest X-ray] or with signs of more generalized pneumonitis.”

Clinical experience

Currently available data indicate that early treatment can reduce the probability that an upper respiratory tract infection caused by community respiratory viruses will progress to viral pneumonia. For example, preliminary results of small, uncontrolled therapeutic trials have suggested that aerosolized ribavirin given preemptively, at various dosages (typically 2 g every

8 hours for 3 to 7 days) either alone or in combination with intravenous immune globulin, to HSCT recipients with symptomatic upper respiratory tract RSV infection decreases the rate of progression to RSV pneumonia.¹⁻³

Dr. Ljungman observed that no controlled studies of therapy for community respiratory viral infections among immunocompromised hosts are published. He also noted that, among the few prospective studies performed, “the definition of outcomes has not been unified” and “there has been no consistency whatsoever in treatment schedules and combinations.”

The European Group for Blood and Marrow Transplantation (EBMT) conducted a prospective study to determine the outcomes of community respiratory viral infections among HSCT recipients.⁴ Of the 46 patients with RSV infections, 29 presented with pneumonia and 17 presented with upper respiratory symptoms, which progressed to pneumonia in 4 of them. The overall mortality rate for RSV infection was 17%; among the 33 patients with RSV pneumonia, it was 39%. Some patients were treated with intravenous (IV) and/or aerosolized ribavirin, some were treated with ribavirin and immunoglobulin (IG), and a few received no antiviral therapy. To better define outcomes, transplant-related mortality due to RSV-associated respiratory failure must be distinguished from that due to other causes. When RSV-associated deaths are considered separately, Dr. Ljungman said, there is a

slight improvement in results with active therapy – either ribavirin or ribavirin/IG – compared with no treatment.

Results of a prospective study of community respiratory viral infections among HSCT recipients and leukemia patients were reviewed by Dr. Richard E. Champlin of the M. D. Anderson Cancer Center.⁵ Dr. Champlin noted that early treatment appears to reduce a patient’s overall chance of developing fatal respiratory tract disease by 40% before engraftment and by 33% after engraftment. In contrast, the mortality rate is very high among patients who are treated late or not at all. “If you’re focusing on advanced infections,” Dr. Champlin noted, “the treatment is probably not going to make much difference, since those patients generally are not going to survive with any available therapy. If therapy is going to make any difference, it is most likely to do so early in the course of the infection. Patients in the peritransplant period have a high rate of progression from upper to lower respiratory infections, which are frequently fatal.” With respect to ribavirin therapy for RSV, Dr. Champlin stated that “our impression is that it does, in fact, help, particularly if given early in the course of the illness,” but he emphasized that no randomized controlled trials have been done.

Studies in progress

Three controlled studies are now under way to better define the preemptive role of antiviral therapy for prevention of viral pneumonia.

This article is based on presentations made at the CME symposium *Community Respiratory Viral Infections in the BMT Population: Update on Prevention and Management*, which was held on February 15, 2001, during the Tandem Meetings of the IBMTR/ABMTR and the American Society for Blood and Marrow Transplantation (ASBMT) at Keystone Resort, Colorado, with the following faculty.

Per Ljungman, MD, PhD (Chair)
 Professor of Hematology
 Head, Department of Hematology
 Huddinge University Hospital
 Karolinska Institutet
 Stockholm, Sweden

Roberta H. Adams, MD
 Clinical Director, Pediatric Blood and Marrow Transplant
 University of Utah/Primary Children’s Medical Center
 Blood and Marrow Transplant Program
 Salt Lake City, Utah

Richard E. Champlin, MD
 Chairman, Department of Blood and Marrow Transplantation
 The University of Texas
 M. D. Anderson Cancer Center
 Houston, Texas

Clare A. Dykewicz, MD, MPH
 Medical Epidemiologist
 National Center for Infectious Diseases
 Centers for Disease Control and Prevention
 Atlanta, Georgia

Janet A. Englund, MD
 Associate Professor
 Department of Pediatrics
 University of Chicago Pritzker School of Medicine
 Chicago, Illinois

W. Garrett Nichols, MD
 Senior Fellow, Infectious Diseases
 Fred Hutchinson Cancer Research Center
 Seattle, Washington

A multicenter randomized study of preemptive treatment with aerosolized ribavirin to prevent progression of RSV upper respiratory tract infection to pneumonia was initiated jointly by the Collaborative Antiviral Study Group and the National Institute of Allergy and Infectious Diseases (NIAID), as Dr. Nichols reported. Eligible patients are HSCT recipients who have undergone transplantation within the preceding 90 days, those who have undergone transplantation within the preceding 180 days if they received cord blood or a transplant from an unrelated donor, and those who are more than 90 days post transplant if they have graft-versus-host disease that requires systemic corticosteroids at a dose greater than 1 mg/kg. The major entry criteria are signs and symptoms of upper respiratory tract infection due to RSV documented by DFA or shell vial culture of a nasopharyngeal wash, without signs of lower respiratory tract infection. At entry, patients are randomized to receive 2 g of aerosolized ribavirin 3 times daily for 10 days or to receive no ribavirin treatment but close daily observation. The primary end point is clinical progression to pneumonia, as assessed by an evaluator masked to the patient's treatment assignment. Secondary end points are DFA- or culture-confirmed RSV pneumonia and safety. Participating centers are now enrolling patients; as of December 2000, 13 patients had been randomized. To achieve a 5% significance level with 80% power, 90 patients will be evaluated (45 in each

treatment arm). This sample size is based on the assumption that the risk for RSV pneumonia will be reduced from 50% to 20% among patients who receive ribavirin. Patients in the study will be stratified by engraftment status and transplant type.

In another study being conducted by the Collaborative Antiviral Study Group and NIAID, patients with RSV pneumonia are randomized to treatment with 2 g of aerosolized ribavirin 3 times daily for 10 days plus either a single 15 mg/kg IV dose of palivizumab (a humanized monoclonal antibody that binds to the RSV F glycoprotein and prevents the virus from infecting the epithelial cells lining the lower respiratory tract) or a palivizumab placebo. As Dr. Nichols reported, the primary end point of this study is all-cause mortality 28 days after randomization. Secondary end points are days of hospitalization, days in the intensive care unit, days of mechanical ventilation, and safety.

Detection before symptoms appear

Dr. Roberta H. Adams of the University of Utah in Salt Lake City discussed a different approach to early detection. This institution's Blood and Marrow Transplant Program seeks to identify patients at high risk for RSV infection before they develop symptomatic disease. Dr. Adams's group conducted a pilot study designed to answer two questions: Is asymptomatic nasal infection with RSV predictive of symptomatic disease, and does treatment of asymptomatic patients decrease the

progression to symptomatic upper or lower respiratory tract disease?⁶ "We wanted to document the incidence of asymptomatic nasal infection in pediatric HSCT patients," Dr. Adams explained, "and then determine the efficacy of giving ribavirin to these patients [to prevent the onset of clinical disease]." During the RSV season, weekly nasopharyngeal washes to detect the presence of RSV were performed on asymptomatic patients. "We tested with an ELISA [enzyme-linked immunosorbent assay] and then confirmed a negative [finding] with a DFA," she said. Patients who tested positive for RSV and could have their transplant postponed were treated with aerosolized ribavirin until nasopharyngeal washes were negative for RSV. Patients who tested positive but could not have their transplant postponed received aerosolized ribavirin and began transplant conditioning.

During this study, 145 nasopharyngeal washes for RSV were performed on 25 patients over two RSV seasons; 10 of the aspirates from 7 asymptomatic patients were positive for RSV. All positive events were successfully treated with ribavirin, which cleared the RSV for a minimum of 3 weeks, and no patient became symptomatic. Two of the 7 patients tested positive for RSV 3 to 4 weeks after the initial course of ribavirin. These patients were retreated with ribavirin and again tested for RSV. One of the 7 patients required two courses of ribavirin before testing negative for RSV. "Our preliminary conclusion was that the use of preemptive

Community respiratory virus guidelines

Prevention

- Restrict exposure of patients to persons with upper or lower respiratory tract infection symptoms
- Conduct active clinical surveillance of all hospitalized patients for community respiratory virus disease

Diagnosis

- Determine etiology of URI using nasopharyngeal wash, swab, or aspirate; throat swab; and/or BAL fluid
- Conduct appropriate diagnostic tests on respiratory samples

Treatment*

- Influenza: Lifelong annual seasonal vaccination starting during the season before HSCT and resuming \geq 6 months after HSCT; chemoprophylaxis with rimantadine or amantadine during influenza A outbreaks
- RSV: HSCT recipients, particularly if pre-engraftment, should have illness diagnosed during URI, and illness should be treated aggressively to prevent fatal disease; strategies include aerosolized ribavirin alone or in combination with RSV immunoglobulin, and RSV monoclonal antibody[†]

BAL = bronchoalveolar lavage; HSCT = hematopoietic stem cell transplant; LRI = lower respiratory infection; URI = upper respiratory infection.

*Data limited to clinical experience.

[†]Multicenter controlled clinical studies are underway to determine optimal therapeutic method (see page 7).

Source: Adapted from Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell recipients. Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation. *MMWR Morb Mortal Wkly Rep* 2000; 49(RR-10): 1-128.

ribavirin in these asymptomatic but RSV-positive patients appeared to limit the onset of clinical disease,” Dr. Adams reported. However, she added, the study did not determine whether these asymptomatic RSV nasal infections would necessarily have progressed to clinical disease. To answer this question, the Pediatric Bone Marrow Consortium is currently recruiting asymptomatic patients with RSV-positive nasal washes into a randomized study that compares aerosolized ribavirin therapy with observation for clinical disease. Any patient in the observation arm who develops evidence of clinical disease will be treated with ribavirin alone or with ribavirin plus RSV IG or palivizumab. The goal is to enroll 54 patients, with 27 patients randomized to each arm.

Prevention and treatment guidelines

The U.S. Center for Disease Control (CDC), in conjunction with the Infectious Diseases Society of America and the ASBMT, recently published guidelines for preventing community respiratory viral infections among HSCT recipients.⁷ In

1997, Dr. Raleigh A. Bowden, a member of the working group that developed the guidelines, described the community respiratory virus experience after marrow transplant from 1990 to 1996 at the Fred Hutchinson Cancer Research Center.¹ As Dr. Clare Dykewicz of the CDC reported, approximately 15% of all patients developed a community respiratory viral infection during each respiratory season from 1990 to 1996. Of these patients, 35% had RSV, 30% had parainfluenza, 25% had rhinovirus, and 11% had influenza. “In this series,” she noted, “pneumonia occurred in 49% of those patients with RSV, 22% of those with parainfluenza, less than 10% of those with influenza, and only 3% of those with rhinovirus infections.” Viral shedding among HSCT recipients with community respiratory viral infection has been reported to last up to 4 months for influenza and up to 20 days for RSV, although RSV viral shedding has been reported to last much longer in some severely immunocompromised patients.

The high rates of infection and the ease with which infectious droplets are spread underscore the importance of preventing exposure of HSCT recipients to

community respiratory viruses. “To minimize the risk for community respiratory virus transmission, [everyone] – specifically, healthcare workers and visitors – with upper respiratory tract infections should be restricted from contact with HSCT recipients and candidates undergoing conditioning therapy,” Dr. Dykewicz emphasized. All hospitalized HSCT recipients and candidates undergoing conditioning therapy should be screened for evidence of community respiratory viral infections; all visitors with upper respiratory symptoms should be asked to defer their visit to the transplant center until their symptoms resolve; and all healthcare workers with symptoms of an upper respiratory tract infection should be restricted from patient contact and reassigned to non-patient care duties until the symptoms resolve.

“RSV is the most important community respiratory virus because it is the most prevalent and also because RSV pneumonia has a case fatality rate of up to 80% in some case series,” Dr. Dykewicz said. The respiratory secretions of any hospitalized HSCT recipient or candidate

Clinical trial recruitment

Two studies mentioned in this article are currently recruiting patients. If you have a patient who may be a candidate, please contact the people listed.

RSV Pediatric BMT Consortium (PBMTC) Trial

A multicenter trial sponsored by the Blood and Marrow Transplant Program at the University of Utah, Salt Lake City (Principal Investigator: Roberta H. Adams, MD, Clinical Director of Pediatric Blood and Marrow Transplant). Non-PBMTC centers are invited to participate.

- **Objectives:** Evaluate the significance of RSV-positive nasopharyngeal wash in *asymptomatic* pediatric BMT patients, and the efficacy and toxicity of preemptive ribavirin therapy in these patients.
- **Major entry criteria:** Patients younger than age 22 who have received a transplant from any stem cell source and have no evidence of upper or lower respiratory tract disease.
- **For more information:** Contact Carolyn Morrison or Marie Fuentes-Rivera at 1-801-585-5270.

A Randomized Phase III Study to Evaluate the Safety and Efficacy of Ribavirin Inhaled Solution in Preventing Progression of Upper Respiratory Tract RSV Infection to RSV Pneumonia in BMT Recipients (CASG-202)

Sponsored by the Collaborative Antiviral Study Group at the University of Alabama (Project Director: Richard J. Whitley, MD) and the National Institute of Allergy and Infectious Diseases, National Institutes of Health. Patients are randomized to either high-dose ribavirin by inhalation therapy or standard treatment. Both groups will receive standard care measures for immunocompromised patients.

- **Objectives:** Test the safety and efficacy of ribavirin aerosol in preventing progression of upper respiratory tract RSV infection to RSV pneumonia in bone marrow and peripheral blood transplant recipients.
- **Major entry criteria:** BMT recipients aged 2 years and older with evidence of upper respiratory tract infection and nasopharyngeal-throat samples positive for RSV who are ≤ 90 days after transplant, or ≤ 180 days after transplant if they received unrelated or cord blood transplant, or > 90 days after transplant if they have graft-versus-host disease requiring > 1 mg/kg of systemic steroids. Patients are not eligible if they are HIV positive, have pneumonia, require a ventilator, or are pregnant, are breast-feeding and unwilling to stop breast-feeding, or are receiving other RSV therapy.
- **For more information:** Contact Richard J. Whitley, MD, University of Alabama at Birmingham, 1600 Seventh Street, Suite 616, Birmingham, AL 35294. Phone: 1-205-934-5316.

who has signs or symptoms of a community respiratory viral infection should be tested promptly with the use of a rapid diagnostic test and viral culture for RSV, even at the time of admission to the transplant center. If two diagnostic samples taken more than 2 days apart do not identify a respiratory pathogen despite persistence of respiratory symptoms, testing of BAL fluid is advised.

"Although a definitive, uniformly effective preemptive therapy for RSV infection among HSCT recipients has not been identified," Dr. Dykewicz said, "certain strategies have been proposed, including use of aerosolized ribavirin, RSV antibodies such as passive immunization with high-titer IVIG, or RSV immunoglobulin in combination with aerosolized ribavirin, and RSV monoclonal antibody." Some researchers report that pediatric HSCT recipients with RSV upper respiratory tract infection or early lower respiratory tract infection can be considered for preemptive therapy with

ribavirin, although this therapy remains controversial. Dr. Dykewicz urged the audience "to participate in randomized, controlled studies to determine the optimal method of RSV control."

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Dr. Eapen Appointed Assistant Scientific Director of Pediatric Cancer Studies

Please give a warm welcome to the newest faculty member of the IBMTR/ABMTR Statistical Center, Mary Eapen, MD, MS, who was recently named Assistant Scientific Director for Pediatric Cancer Studies. Dr. Eapen has a primary appointment with the Medical College of Wisconsin Division of Pediatric Hematology/Oncology where she is an attending transplant physician. Dr. Eapen received her medical degree from Ahmadu Bello University in Nigeria and trained in Pediatrics at University Hospital of Wales, Cardiff and the Royal Manchester Children's Hospital in Manchester, England. She became interested in oncology and bone marrow transplantation at Manchester and relocated to Minneapolis to join the Oncology/BMT fellowship program at the University of Minnesota in 1997. While at the University of Minnesota, she completed her fellowship in Pediatric Oncology/Blood and Marrow Transplantation as well as her MS in Clinical Research.

Dr. Eapen's research interests focus on outcomes after blood and marrow transplantation in children, including long-term outcomes and quality of life. She serves as the primary biostatistician for the IBMTR/ABMTR Immune Disorders / Metabolic Deficiencies and Pediatric Cancers Working Committees.

Dr. Eapen was recently awarded an American Society of Clinical Oncology Clinical Research Career Development Award. This three-year grant will fund Dr. Eapen's research in outcomes after transplantation for acute leukemias in children. Dr. Eapen will use the information in the IBMTR/ABMTR database to study transplantation in children with high-risk acute leukemia. These studies focus on clinical situations where small numbers of patients preclude large prospective studies. Dr. Eapen's studies aim to determine: (1) whether leukemia-free survival is higher with unrelated umbilical cord blood transplantation than with autologous stem cell transplantation for acute leukemia in first or second remission; (2) the efficacy of second transplantation as salvage therapy for acute lymphoblastic or myelogenous leukemia after a first bone marrow transplant from an HLA-identical sibling; and (3) the influence of preparative regimens on the outcome of allogeneic bone marrow transplantation for juvenile myelomonocytic leukemia.

Dr. Eapen's unique combination of skills as a pediatric clinical specialist along with her expertise in statistical data analysis will add to the quality and productivity of the Registries' pediatric cancer research program.

NIH Grant Awarded to Develop a Blood and Marrow Transplant Clinical Trials Network

The IBMTR/ABMTR, in collaboration with the National Marrow Donor Program® and EMMES Corporation®, was recently awarded a five-year NIH grant to coordinate a newly-established Blood and Marrow Transplant Clinical Research Network (BMT CTN). Funding for this Network is being provided by both the National Heart, Lung and Blood Institute and the National Cancer Institute. Our consortium is establishing a Data Coordinating Center for a national network of centers carrying out clinical trials focused on hematopoietic stem cell transplantation. Additional goals of the consortium include the development of consensus guidelines for diagnosing, monitoring and grading important transplant-related endpoints and the development and use of novel study designs to increase the efficiency and scientific validity of clinical trials in blood and marrow transplantation. The NIH also awarded grants to fourteen transplant centers/consortia to participate in this Network as core clinical centers.

The Wonderful Hospitality of the People of Newfoundland

By **Dr. Alberto Marmont du Haut Champ**

Emeritus Professor of Hematology, S Martino's Hospital, Genoa, Italy

On the early morning of September 11, Dr. Francesca Gualandi and I flew from Genoa, Italy to Paris, and then boarded Delta Flight 145 to Atlanta. We were subsequently to fly to Salt Lake City, and from there to Snowbird, Utah, to take part in a conference on stem cell therapy for autoimmune diseases.

The flight was smooth, but suddenly we were told by the captain that US air space was closed and we would be landing at St John's, Newfoundland.

While we were anxiously, and finally wearily, waiting for instructions, all of Canada, all of Newfoundland, and more specifically all of St John's were mobilizing and organizing a gigantic effort to receive the huge numbers of airplanes and passengers that had landed on their soil.

It was hard to be instructed to leave all our belongings, except essential medications, on the plane. However, we were whisked through customs, briskly embarked in a flotilla of buses and taken to the cavernous Mile One Stadium. Again the atmosphere was cheerful, and friendly cries of welcome were resounding from all sides.

How many hours that night, and in all the days that were to come, I spent in Mile One Stadium watching TV and waiting for information, I cannot remember. But what impressed me was the row of telephones almost immediately provided for free use. I am still amazed at how people managed to do it, how they reached an agreement with the companies, how you just dialed your rosary of digits and pronto, you were speaking with home. A nice combination of technology and human solidarity, indeed.

From the Mile One Stadium we were bused to the Salvation Army's Church. There many things greeted us, but first of all friendly smiles, and again this wonderful feeling of arriving among friends who are happy to meet you in the small hours of the night, when sensible people are soundly asleep in their beds.

What the Salvation Army did for us is almost impossible to relate. I regret not having taken note of everybody. Let Danny and Lori Pickens receive our thanks and extend them to all the others. And let me also remember the little girl who came up to me and solemnly handed me a cardboard sheet where she had designed an airplane and three welcomes.

The Salvation Army had prepared rows of cots, and Francesca Gualandi took advantage of one of them. My tired bones were shuddering at the thought of lying on hard concrete, when out of nowhere came Mark, who most pleasantly invited two distinguished American couples from Atlanta and myself to come and sleep for the rest of the night at his place. It was a great comfort. Thank you, Mark and Jason, for your friendly hospitality.

On the following day, no flights but a nice visit to St John's, and to the bronze plaque that commemorates Marconi's epochal wireless message between Ireland and Newfoundland. In the evening Patricia and Wallace Viguers without hesitation invited a group to stay in their house. There then followed two days of the Viguers' wonderful hospitality: comfortable beds, excellent breakfasts, fascinating sightseeing tours.

There was some frustration on September 15 when we were sitting on our plane waiting for takeoff and our captain almost sorrowfully told us a small aircraft had crashed (thankfully there were no serious injuries) and obstructed the main runway. Disembarkation in rain and wind (Hurricane Erin, if I remember correctly) and another night in a hotel in St John's (a vacancy, at long last).

Back home via Atlanta and Rome two feelings persist – horror at the dastardly assaults and gratitude for the warm and friendly hospitality. These few words have been written to thank all of you, my friends of Newfoundland.

Quality of life and relationships after stem cell transplantation



J. Douglas Rizzo, MD

Assistant Scientific Director, IBMTR/ABMTR,
Assistant Professor of Medicine, Medical College of Wisconsin, Milwaukee

As supportive care for stem cell transplantation improves, more patients are becoming long-term survivors than ever before. Consequently, it is increasingly important to understand the long-term consequences of transplantation, including the impact on quality of life of these survivors.

Previous studies report varying levels of health-related quality of life (physical endurance, emotional well-being, concentration, sexuality, relationships) in survivors at different times post-transplantation. However, these results are of limited value because of small numbers of patients, lack of control groups, and non-standard measures of quality of life.

The IBMTR/ABMTR, together with investigators at the University of Florida (led by John Wingard and Michelle Bishop), the Evanston Northwestern Hospital (ENH) in Illinois (led by David Cella) and the University of Kentucky (Michael Andrykowski), is currently conducting a large quality-of-life study. The goal is to interview 800 survivors who received stem cell transplantation for one of several diseases, as well as 200 spouses and 200 acquaintance controls. The study is being carried out in cooperation with 44 transplant centers throughout the United States and Canada. The objectives of the study are to:

1. characterize the quality of life of adult transplant recipients
2. identify demographic and clinical variables associated with post-transplant quality of life outcomes and;
3. test a psychosocial model of coping to account for differences in interpersonal relationships and psychological growth.

Eligible patients include recipients of allogeneic or autologous stem cell transplants, who are alive at least one year post-transplant without evidence of primary disease recurrence. Based on updated follow-up information provided by participating centers, patients are randomly selected by the IBMTR for recruitment Staff at each participating center then contact the selected patients to discuss the study. Once a patient consents to the study, medical follow-up is arranged to ascertain current

physical health. Patient contact information is forwarded to ENH. ENH mails a packet of written questionnaires to the patient, and arranges a time to conduct a telephone interview. The written questionnaires and the telephone interview each take about 45 minutes to complete. The questionnaire and telephone interview will be used to carry out a comprehensive assessment of the patient's quality of life, relationships, coping and adjustment mechanisms, and the role each plays in the patient's current life.

Thanks to the team of dedicated recruiters at each of the participating centers, we have already enrolled more than 400 patients to the study since August 2000. More than 300 of these patients have completed the questionnaire and telephone interview. It is encouraging that more than 90% of patients contacted consent to participate, and, of the patients who consent, most complete all aspects of the study. In fact, many patients appreciate the opportunity to describe their transplant experience and its impact on their lives. Site coordinators also describe the experience of talking with survivors as positive and rewarding.

With this much information gathered the team of investigators is looking forward to performing preliminary analyses for presentation at the ASH 2001 meeting, as well as the 2002 IBMTR/ABMTR annual meeting in Orlando. By understanding factors that appear to place patients and their partners at risk for poor physical, emotional, social, sexual and functional quality of life, we hope to make recommendations to transplant centers that may reduce the likelihood of survivors having a poor quality of life. In addition, we are exploring factors that may contribute to patient and partner resilience and growth, so survivors may lead a more satisfying life, regardless of the complications they may experience.

Our thanks to all who are part of this study, especially the study coordinators at participating centers who are critical to its success.

Celebrating Life Calendar 2002

The IBMTR/ABMTR is proud to be a supporter of the Celebrating Life Calendar 2002, being produced by the Blood & Marrow Transplant Information Network. BMT InfoNet provides reliable information and emotional support to thousands of HSCT patients and survivors each year. The Celebrating Life calendar celebrates 13 miracles – ten adults, one teen and two little brothers who underwent a bone marrow or blood stem cell transplant. They survived to embrace life with joy and pleasure. The calendar shares the uplifting stories of these survivors and will raise funds for the patient services provided by the BMT Information Network. For more information on purchasing the Celebrating Life calendar to aid this worthy cause, please contact BMT InfoNet at **874-433-3313** or **help@bmtinfonet.org**. Calendars are \$10 each, plus shipping and handling, and can also be ordered via the BMT InfoNet web site, **www.bmtinfonet.org**.

Foundation and corporate support of the IBMTR/ABMTR

Thanks to the many contributors who have joined our international collaboration for research in blood and marrow transplantation. We gratefully acknowledge the support of the Medical College of Wisconsin; the National Cancer Institute; the National Institute of Allergy and Infectious Disease; the National Heart, Lung and Blood Institute; the Department of Defense; and the generosity of the following supporters:

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The Mortimer M. Bortin Memorial Fund

The Mortimer M. Bortin Memorial Fund was created as a memorial to Dr. Mortimer M. Bortin, principal founder of the IBMTR. The Fund is a tribute to Dr. Bortin's vision of "Sharing Knowledge, Sharing Hope" – transplant centers around the world sharing and collaboratively analyzing patient outcomes information in order to more effectively treat future transplant patients.

Our gratitude goes to those who share not only their transplant data but also their financial resources in order to allow the IBMTR/ABMTR to complete the more than 80 studies the Statistical Center is currently coordinating. Because we are a non-profit organization, we must rely heavily on private grants

and donations to fund our new programs and research initiatives so that physicians worldwide and their patients receive timely data regarding transplant treatment regimens and outcomes. Please help us continue to make a difference in the lives of those suffering from cancer and other life-threatening conditions. A gift of any size to the IBMTR/ABMTR Statistical Center truly helps our efforts to share our research and bring new hope for improved medical treatments in blood and marrow transplantation. Thank you for your important participation in our promising future.

For information on supporting the research of the IBMTR/ABMTR, please contact Lisa Schneider, Associate Director of Development, Tel: **414 456-8363**, E-mail: schneide@mcw.edu.

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