



Annotated Bibliography

XIV. Adverse Events in Cord Blood Transplantation



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i. Infections (Other than EBV)

1. **Umbilical cord blood transplantation and cytomegalovirus: Posttransplantation infection and donor screening.** Albano MS, Taylor P, Pass RF, Scaradavou A, Ciubotariu R, Carrier C, Dobrila L, Rubinstein P, Stevens CE. *Blood*. 2006;108:4275-4282.

Abstract

This study assessed the incidence of cytomegalovirus (CMV) infection after transplantation of cord blood (CB) from unrelated donors and evaluated strategies for screening CB donors. Posttransplantation CMV infection, reported in 23% of 1221 CB recipients, was associated with patient pretransplantation CMV serology ($P < 0.001$), but not with CMV serology in CB donors or their mothers.

A total of 26,988 CB donors were evaluated by viral culture of saliva. Subgroups were evaluated by polymerase chain reaction in CB (CB-PCR) in 2 case-control studies. In the first study, 33 of 47 saliva culture-positive CB donors were confirmed by CB-PCR. All mothers of the 33 infants with confirmed CMV infection were CMV-total antibody positive, but only 1 of 3 had CMV-IgM antibody. The second study evaluated infants born to mothers with CMV-IgM antibody. Of these, 5 of 170 saliva culture-negative infants were positive by CB-PCR. The incidence of congenital CMV infection in CB donors was low (0.12%). Maternal serology had poor predictive value for CMV infection in their infant CB donors and bore no detected relationship to CMV infection in CB recipients. Saliva culture for CMV had both false-positive and -negative results. CB-PCR was a useful alternative for detecting CMV in CB donors.

If testing CB donors for evidence of CMV infection remains mandated by the FDA, despite its low prevalence in newborns and despite the fact that traditional serologic screening methods are not very informative in CB, a practical strategy to detect the virus would be needed that takes into account specificity and sensitivity as well as cost and logistics. Detection of CMV DNA in CB by nucleic acid testing, as shown in this study, can be reliable, sensitive and specific. The fact that confirmed congenital CMV infections were limited to infants of antibody-positive mothers suggests a potential screening strategy based on testing mothers for antibodies to CMV followed by prerelease testing of CB units for CMV DNA by PCR when the mother is antibody positive, regardless of her IgM anti-CMV status. However, any strategy to detect infection in the CB donor is hampered by the lack of an FDA-approved assay to screen CB donors.

2. **Umbilical cord blood transplantation and cytomegalovirus: post-transplant infection and donor screening.** Maria S Albano, Patricia Taylor, Robert F Pass, Andromachi Scaradavou, Rodica Ciubotariu, Carmelita Carrier, Ludy Dobrila, Pablo Rubinstein, and Cladd E Stevens. *Blood* 2006;108:4275-82. [Abstract](#)

CB is presumed to have a low risk of transmitting CMV because of the low rate of congenital CMV infection (0.2-2.5% of U. S. births). However, no previous study has systematically assessed the risk of CMV infection in CB transplant recipients or has evaluated the effectiveness of methods to screen CB donors in this context.

This study assessed the incidence of cytomegalovirus (CMV) infection after transplantation of cord blood (CB) from unrelated donors and evaluated strategies for screening cord blood donors. A total of 26,988 infant CB donors were evaluated by viral culture of saliva.

Unlike studies of BMT, **post-transplant CMV infection in CB recipients in this study had no detected association with donor serology** (i.e., the donor mother's CMV antibody status). Even when the donor's mother was IgM anti-CMV, there was no association with post-transplant CMV. These data support the view that CB units need not be excluded for transplantation based on the donor's maternal CMV serological results alone.

The incidence of congenital CMV infection in CB donors in this study was 0.12% by positive saliva culture and confirmed CB-PCR, and the authors suggest that **this low incidence might predict a lower overall incidence of post-transplant CMV infection in CB recipients than in recipients of BM/PBSC grafts.** Indeed, the incidence in antibody negative recipients was only 8% (presumably nearly all acquired from some source other than the CB graft).

Most of the CB donor infants in this study who had a positive saliva culture had their infection confirmed by detection of CMV-DNA in CB by PCR. Some presumed infections, however, were not confirmed by PCR and the data suggest that the culture positive infants with a PCR-negative CB most likely had a false positive saliva culture. It is also true that a saliva culture may have missed some congenital CMV infections.

The positive predictive value for congenital CMV infections confirmed by CB-PCR was 3.8% for infants born to IgM positive mothers and only 0.2% when the mother was total anti-CMV positive (regardless of IgM status). Thus, a screening strategy based on antibody positivity in the donor's mother would unnecessarily exclude a large number of CB units, the vast majority of which have no risk of CMV transmission to recipients. Also, screening for maternal IgM anti-CMV alone would miss two-thirds of infections.

If testing of CB donors for evidence of CMV infection remains mandated by the FDA despite its low prevalence in newborns and despite the fact that traditional serologic screening methods are not very informative in CB, a practical strategy to detect the virus would be needed that takes into account specificity and sensitivity as well as cost and logistics. **The authors suggest that testing the CB graft itself for CMV-DNA by nucleic acid-based methods can be reliable, sensitive and specific.** The fact that confirmed

congenital CMV infections were limited to infants of antibody positive mothers suggests a potential screening strategy based on testing mothers for antibodies to CMV followed by pre-release testing of CB units for CMV-DNA by PCR when the mother is antibody positive. At present, any strategy to detect infection per se in the CB donor is hampered by the lack of an FDA-approved assay to screen CB donors.

3. **Update on management of infections in cancer and stem cell transplant patients.** Neuburger S, Maschmeyer G. *Ann Hematol.* 2006;85:345-56. **Abstract**

This is a very useful detailed **review** of infections in patients with hematological malignancies. The authors indicate that, in the past two decades, the epidemiology of febrile episodes in neutropenic patients has changed profoundly. Gram-negative bacterial such as *Pseudomonas aeruginosa* or enterobacteria have been dominating in microbiologically proven infections two decades ago, gram positive cocci are now by far the most frequently isolated pathogens in many cancer centers. Up to now, *C. albicans* remains the most common fungal pathogen in patients with hematological and oncological malignancies. However, infections by *non-albicans* species, such as *Candida glabrata*, *Candida parapsilosis*, *Candida krusei* or *Candida tropicalis* have become more frequent. In high risk patients, the incidence of invasive pulmonary aspergillosis (IPA) has increased continuously, and IPA is often life-threatening with survival rates of less than 15% having been reported among patients undergoing allogeneic stem cell transplantation.

The **key risk factor** for the emergence and the clinical course of fever and infection is the **extent and duration of neutropenia**. Patients with neutropenia lasting for less than 5-7 days, who have no additional risk factors such as open wounds, tumor-associated airway or bile obstruction are regarded as **low-risk patients**. In contrast, patients with aggressive hematological malignancies undergoing intensive chemotherapy have an expected duration of profound neutropenia of at least 10 days and are therefore categorized as a **high-risk group**.

In more than 50% of febrile episodes, the source of the infection cannot be identified. In **low-risk patients**, recently revised guidelines have recommended outpatient management with administration of oral empirical antimicrobial therapy with ciprofloxacin plus amoxicillin-clavulanate. **Patients with high or intermediate risk should unequivocally be treated with intravenous antimicrobial therapy**. Guidelines by the Infectious Diseases Society of America (IDSA) recommend monotherapy with cefepime or a carbapenem (meropenem, imipenem-cilastatin) or duotherapy without an antipseudomonal beta-lactam antibiotic plus an aminoglycoside as appropriate choices for initial empirical therapy in this setting. Several double-blind, placebo-controlled trials have shown that piperacillin-tazobactam may also be efficacious and that a combination with an aminoglycoside is not required. Fluoroquinolones such as ciprofloxacin are not recommended for initial empirical intravenous monotherapy because of inferior efficacy and the emergence of resistance among gram-negative bacilli. This publication goes on to review diagnostic and therapeutic approaches to patients with pulmonary infiltrates, catheter-related infections, abdominal infections, pneumocystis pneumonia, bacteremia and fungal infections. In patients with lung infiltrates, early preemptive intervention with an antifungal active against aspergilli is recommended, whereas in patients with catheter-related, skin or soft tissue infections, preemptive addition of a glycopeptide shows a high response rate. Dosages of antimicrobial drugs for adult patients are provided in a table.

Finally, methods of prevention, diagnosis and treatment of CMV infections are reviewed. The prompt preemptive use of ganciclovir or foscarnet in allogeneic stem cell transplant recipients can reliably be guided by serial monitoring of cytomegalovirus antigen and polymerase chain reaction monitoring.

4. **Severe Infections after Unrelated Donor Allogeneic Hematopoietic Stem Cell Transplantation in Adults: Comparison of Cord Blood Transplantation with Peripheral Blood and Bone Marrow Transplantation.** Rocío Parody, Rodrigo Martino, Montserrat Rovira, Lourdes Vazquez, María José Vázquez, Rafael de la Cámara, Cristina Blazquez, Francesc Fernández-Avilés, Enric Carreras, Miguel Salavert, Isidro Jarque, Carmen Martín, Francisco Martínez, Javier López, Antonio Torres, Jorge Sierra, Guillermo F. Sanz *Biology of Blood and Marrow Transplantation* 2006;12:734-748. **Abstract**

The authors evaluated the occurrence of severe infections in 192 consecutive adult recipients of volunteer unrelated donor allogeneic hematopoietic stem cell transplants, with a detailed **analysis of severe infections after receipt of cord blood transplants (CBTs; n = 48) or bone marrow transplants (BMTs)/peripheral blood stem cell transplants (PBSCTs; n = 144)**.

At a 3-year median follow-up, CBT recipients had a higher risk of developing any severe infection (85% versus 69% in BMT/PBSC recipients, $P < .01$). CBT recipients had a higher incidence of severe bacterial infections before day +100, but at 3 years the risks of these and other infections were similar in the CBT and BMT/PBSC groups. In addition, the 100-day and 3-year incidences of infection-related mortality (IRM) did not differ between groups ($P = .2$ and $.5$, respectively). In multivariate analysis, the most significant risk factor for IRM in all 192 patients was monocytopenia ($.2 \times 10^9/L$). In CBT recipients, only neutropenia ($.2 \times 10^9/L$) on day +30 and low nucleated cell dose infusion ($<2 \times 10^7/kg$) showed a trend for increased IRM ($P = .05$ in both cases). Stem cell source had no effect on day +100 or 3-year non-relapse mortality (NRM), cytomegalovirus infection, cytomegalovirus disease (7% versus 6%), or overall survival (36% versus 39%, respectively). The number of mismatches in HLA (A, B, and DRB1) had no effect on any outcome in CBT recipients. In contrast, in the BMT/PBSC group, the presence of any mismatch by low or high-resolution HLA typing (A, B, C, and DRB1) increased NRM and decreased overall survival ($P < .01$). IRM was the primary or secondary cause of death in 61% and 59% of CBT and BMT/PBSC recipients who died, respectively.

The authors concluded that their results confirm the relevance of severe infectious complications as source of severe morbidity and NRM after volunteer unrelated donor hematopoietic stem cell transplantation in adults, but suggest that **CBT recipients have a similar risk of dying from an infection if an accurate selection of a cord blood unit is done**.

5. **Serious infections after unrelated donor transplantation in 136 children: impact of stem cell source.** Barker JN, Hough RE, Van Burik JA, Defor TE, Macmillan ML, O'Brien MR, Wagner JE. *Biol Blood Marrow Transplant.* 2005;11:362-70. **Abstract**

The authors compared serious infections in the 2 years after pediatric myeloablative unrelated donor transplantation with unmanipulated BM (n = 52), T cell-depleted (TCD) BM (n = 24), or umbilical cord blood (UCB) (n = 60) for the treatment of hematologic malignancy. Overall, the cumulative incidence of 1 or more serious infections was comparable between groups (BM, 81%; TCD, 83%; UCB, 90%; $P = .12$). Furthermore, by taking all serious infections into account and using multivariate techniques with unmanipulated BM as the reference, there were also no significant differences between groups (TCD relative risk (RR), 1.6; $P = .10$; UCB RR, 1.0; $P = .84$). Within the time periods days 0 to 42, days 43 to 100, and days 101 to 180, the only difference was a greater risk of viral infections from days 0 to 42 in TCD recipients (RR, 3.5; $P = .02$). Notably, after day 180, TCD recipients had a significantly increased infection risk (RR, 3.1; $P = .03$), whereas the risk in UCB recipients (RR, 0.5; $P = .23$) was comparable to that in BM recipients. Other factors associated with an increased infection risk in the 2 years after transplantation were age ≥ 8 years, graft failure, and severe acute graft-versus-host disease.

The authors conclude that their data suggest that the risk of serious infection after pediatric UCB transplantation is comparable to that with unmanipulated BM.

6. **Bloodstream infection after umbilical cord blood transplantation using reduced-intensity stem cell transplantation for adult patients.** Narimatsu H, Matsumura T, Kami M, Miyakoshi S, Kusumi E, Takagi S, Miura Y, Kato D, Inokuchi C, Myojo T, Kishi Y, Murashige N, Yuji K, Masuoka K, Yoneyama A, Wake A, Morinaga S, Kanda Y, Taniguchi S. *Biol Blood Marrow Transplant.* 2005;11:429-36. [Abstract](#)

The frequency of bacterial infection after allogeneic hematopoietic stem cell transplantation (allo-SCT) has decreased with the widespread use of antimicrobial prophylaxis and empirical administration of broad-spectrum antimicrobials. However, better control of gram-negative infections in neutropenic patients has fostered the increase of infections caused by gram-positive organisms and also gram-negative organisms resistant to β -lactams or fluoroquinolones. These organisms now account for most bacterial infections.

The authors retrospectively reviewed the medical records of 102 adult patients who received RI-CBT for advanced hematologic disease to determine the frequency and clinical features of bacteremia. The median age of the patients was 55 years (range, 17-79 years). Preparative regimens comprised fludarabine 125 to 150 mg/m², melphalan 80 to 140 mg/m², or busulfan 8 mg/kg and total body irradiation 2 to 8 Gy. Prophylaxis against graft-versus-host disease comprised cyclosporin or tacrolimus. BSI developed within 100 days of RI-CBT in 32 patients. The cumulative incidence of BSI was 25% at day 30 and 32% at day 100. The median onset was day 15 (range, 1-98 days). Causative organisms included *Pseudomonas aeruginosa* (n = 12), *Staphylococcus epidermidis* (n = 11), *Staphylococcus aureus* (n = 6), *Enterococcus faecium* (n = 4), *Enterococcus faecalis* (n = 4), *Stenotrophomonas maltophilia* (n = 4), and others (n = 7). Of the 32 patients with BSI, 25 (84%) died within 100 days after RI-CBT. BSI was the direct cause of death in 8 patients (25%). Univariate analysis failed to identify any significant risk factors.

The authors state that the incidence of BSI was 20-30% after reduced-intensity stem cell transplantation from an HLA-identical related donor which is comparable to their results after RI-CBT. Also, the incidences after myeloablative allo-SCT from a matched sibling or matched unrelated donor were slightly higher (40-50%).

BSI clearly represents a significant and fatal complication after RI-CBT. Further studies are warranted to determine clinical characteristics, identify patients at high risk of BSI, and establish therapeutic strategies.

7. **Early infections in adult patients undergoing unrelated donor cord blood transplantation.** Saavedra S, Sanz GF, Jarque I, Moscardo F, Jimenez C, Lorenzo I, Martin G, Martinez J, De La Rubia J, Andreu R, Molla S, Llopis I, Fernandez MJ, Salavert M, Acosta B, Gobernado M, Sanz MA. *Bone Marrow Transplant.* 2002;30:937-943. [Abstract](#)

The authors studied the incidence and characteristics of early infections (before day 100) in a series of 27 adult patients (median age 30 years, range 16-46) undergoing UD-CBT at a single institution. All 27 patients experienced at least one infectious episode and 18 (66%) suffered a severe infection. Bacteremia occurred in 55% of patients (13 with Gram-positive and 11 with Gram-negative microorganisms). Eleven of 19 CMV-seropositive patients (58%) developed CMV antigenemia and one patient had CMV disease. Fungal infections were documented in three patients (11%), comprising invasive fungal infections in two cases and a localized esophagitis in one. Ten patients (37%) died before day 100 after transplantation. Infection was considered the primary cause of death in four patients (sepsis by *Acinetobacter* spp. bacteremia in three cases) and contributed to death in another four. The most striking findings in this series were the high incidence of, and mortality due to multiresistant *Acinetobacter* spp. and the low incidence of and lack of mortality due to CMV disease. This report confirms that infection is a major complication in adults undergoing UD-CBT.

8. **Cytomegalovirus infection following unrelated cord blood transplantation for adult patients: a single institute experience in Japan.** Tomonari A, Iseki T, Ooi J, Takahashi S, Shindo M, Ishii K, Nagamura F, Uchimaruk K, Tani K, Tojo A, Asano S. *Br J Haematol.* 2003;121:304-311. [Abstract](#)

Cytomegalovirus (CMV) infection in 28 adult patients after cord blood transplantation (CBT) from unrelated donors was compared with that after bone marrow transplantation from HLA-matched related (R-BMT) and unrelated (U-BMT) donors. Positive CMV antigenaemia was seen in 19 (79%) of 24 CMV-seropositive patients at a median of 42 d (range 29-85 d) after CBT, but in zero of four CMV-seronegative patients. This did not differ significantly from values observed after R-BMT and U-BMT (66%, P = 0.22, and 60%, P = 0.15 respectively). Based on the antigenaemia results, 16 patients (67%) received pre-emptive ganciclovir therapy from a median of 47 d (range 36-67 d) after CBT. This proportion was higher than that observed after R-BMT (28%, P = 0.0048), but did not differ from that after U-BMT (50%, P = 0.21). In addition, the probability of requiring more than two courses of ganciclovir therapy after CBT (21%) was higher than after R-BMT and U-BMT (0%, P = 0.015 and 0.039 respectively). One patient (5%) developed CMV disease after U-BMT, whereas no patients developed CMV disease after CBT or R-BMT.

9. **High incidence of cytomegalovirus reactivation in adult recipients of an unrelated cord blood transplant.** Takami A, Mochizuki K, Asakura H, Yamazaki H, Okumura H, Nakao S. *Haematologica.* 2005;90:1290-2. [Full Text](#)

Cytomegalovirus (CMV) infection is still a major concern following allogeneic HSCT because CMV pneumonia is fatal in 70% of patients.

The authors performed a retrospective study of CMV reactivation and infection following HSCT. **Eighty-four consecutive adult patients who were CMV-seropositive and who had successful initial engraftment were analyzed, including 10 umbilical cord blood transplant patients.**

Results indicated that CMV antigenemia occurred after transplantation in 10/10 (100%) recipients of unrelated cord blood, 17/39 (43%) recipients of a related matched donor graft, 16/23 (79%) recipients of an unrelated matched donor graft, and 8/12 (67%) recipients of a mismatched related donor graft. CMV-associated disease occurred in three patients (4%), including **one of the 10 UCBT patients who developed interstitial pneumonia and died of CMV disease.** On the basis of these results **the authors suggest that unrelated cord blood transplantation may be correlated with a high incidence of CMV reactivation.**

10. **Varicella-zoster virus infection in adult patients after unrelated cord blood transplantation: a single institute experience in Japan.** Tomonari A, Iseki T, Takahashi S, Ooi J, Takasugi K, Shimohakamada Y, Ohno N, Nagamura F, Uchimaruk K, Tani K, Tojo A, Asano S. *Br J Haematol.* 2003;122:802-5. [Abstract](#)

Varicella-zoster virus (VZV) infection was studied in 40 adult patients who underwent cord blood transplantation (CBT) from unrelated donors. Twenty-five patients developed VZV reactivation at a median of 5 months after CBT (range 1.7-26 months). The cumulative incidence of VZV reactivation after CBT was 80% at 30 months. Twenty-two patients developed localized herpes zoster. The remaining three patients developed atypical non-localized herpes zoster, which was associated with visceral dissemination in one patient. All the patients responded well to antiviral therapy. Unexpectedly, the absence of grade II-IV acute graft-versus-host disease (GVHD) was associated with a higher rate of VZV reactivation after CBT (100% versus 55%, P=0.01). These results suggest

that recovery of VZV-specific immune responses after CBT is delayed even in patients without severe acute GVHD.

11. **Ganciclovir-related neutropenia after preemptive therapy for cytomegalovirus infection: comparison between cord blood and bone marrow transplantation.** Tomonari A, Iseki T, Takahashi S, Ooi J, Yamada T, Takasugi K, Nagamura F, Uchimaru K, Tojo A, Asano S. *Ann Hematol.* 2004;83:573-7. [Abstract](#)

The authors studied ganciclovir (GCV)-related neutropenia after preemptive therapy for cytomegalovirus infection: 9 of 17 (53%) cord blood transplantation (CBT) patients and 18 of 20 (90%) bone marrow transplantation (BMT) patients developed GCV-related neutropenia with an absolute neutrophil count (ANC) of less than 1000/microl. The incidences of neutropenia in patients with an ANC of less than 1000, 500, and 250/microl were significantly lower after CBT in comparison with BMT. Two BMT patients, but no CBT patients, developed neutropenic fever, and both patients recovered after antibiotic therapy. In CBT patients, a creatinine clearance rate of less than 50 ml/min and an absence of steroid therapy were associated with a greater incidence of GCV-related neutropenia. No risk factors for GCV-related neutropenia were found in BMT patients. The authors concluded that these results suggest that GCV may be less toxic to myeloid progenitor cells from cord blood than those from bone marrow.

12. **Risk of transmission of herpesviruses through cord blood transplantation.** Weinberg A, Enomoto L, Li S, Shen D, Coll J, Shpall EJ. *Biol Blood Marrow Transplant* 2005;11:35-8. [Abstract](#)

There is concern that cord blood (CB) transplants might carry a higher risk of opportunistic infections. Human herpesviruses (HHV) are common pathogens in transplant recipients. To assess the incidence of beta and gamma HHV infection of CB collected under standard procedures, the authors tested 362 CB samples for the presence of CMV; HHV-6, -7, and -8; and Epstein-Barr virus DNA by polymerase chain reaction. HHV-6 DNA was found in 2 samples, yielding an incidence of 0.55% (95% confidence interval, 0.1%-2%). None of the other viral DNAs was found, resulting in a 95% confidence interval of 0% to 1% for the incidence of CMV, Epstein-Barr virus, HHV-7, and HHV-8. The authors state that their data show that the routine screening prospective CB donors with anti-CMV immunoglobulin M practically eliminates the risk of CB CMV transmission, but state that HHV-6 warrants CB testing by polymerase chain reaction. They also indicate that, because the seroprevalence of HHV-8 among the CB donors in this study was only 4%, these findings cannot be extended to HHV-8-endemic areas.

13. **Disseminated tuberculosis following reduced-intensity cord blood transplantation for adult patients with hematological diseases.** Maeda T, Kusumi E, Kami M, Kawabata M, Le Pavoux A, Hara S, Chizuka A, Murashige N, Tanimoto TE, Matsumura T, Yuji K, Wake A, Miyakoshi S, Morinaga S, Taniguchi S; Tokyo Stem Cell Transplant (SCT) Consortium. *Bone Marrow Transplant.* 2005;35:91-7. [Abstract](#)

The authors retrospectively reviewed medical records of 113 adult patients with a median age of 54 years who underwent reduced-intensity UCBT (RI-UCBT) at Toranomon Hospital from March 2002 to May 2004. Mycobacterium tuberculosis infections were diagnosed in three patients (2.7%), of these two patients developed primary infection and one patient developed reactivation of latent tuberculosis. The interval between RI-UCBT and the diagnosis of tuberculosis was 34, 41 and 61 days. All the patients had disseminated disease at diagnosis. Histological examination showed the lack of granuloma in caseous necrosis. Combination antituberculous treatments showed limited efficacy, and two patients died immediately after diagnosis. *M. tuberculosis* caused life-threatening illness, rapidly progressing in RI-UCBT recipients. The lack of granuloma in caseous necrosis suggests the impaired T-cell function in early post transplant phase of RI-UCBT. *M. tuberculosis* should be considered in the differential diagnoses of fever of unknown source after RI-UCBT.

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