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High-dose chemotherapy

Less frequent catheter dressing changes decrease local cutaneous toxicity of high-dose chemotherapy in children, without increasing the rate of catheter-related infections: results of a randomised trial

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Summary:

Cutaneous lesions caused by catheter dressing changes can be serious and generate local pain in children undergoing high-dose chemotherapy followed by bone marrow transplantation. One hundred and thirteen children entered a randomised trial to compare two catheter dressing change frequencies (15 days *vs* 4 days). Skin toxicity was classified according to the following scale: grade 0: healthy skin, to grade 4: severe skin toxicity. A qualitative culture of the skin at the catheter entry site was taken whenever the dressing was changed. Of the 112 evaluable children (56 in each group) 32 developed grade ⩾2 local skin toxicity (eight in the 15-day group and 24 in the 4-day group; $P = 0.001$). Although higher in the 4-day group, the proportions of children experiencing pain during and between dressing changes were not statistically different between the two groups. The proportion of patients with one or more positive skin culture(s) at the catheter entry site during hospitalisation were similar in the two groups (27% in the 15-day group and 23% in the 4-day group) as were the proportions of documented nosocomial bloodstream infections (11% and 13%; NS). Whereas the planned frequency was maintained in the 4-day group (mean = 4 days, s.d. = 1), it was usually shortened in the 15-day group (mean = 8 days, s.d. = 4), mainly because dressings had loosened. Decreasing the catheter dressing change frequency proved efficient in reducing cutaneous toxicity without increasing the risk of local and systemic infection. In our unit, catheter dressings are changed every 8 days since this analysis.
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In our hospital, patients treated with high-dose chemo/radiotherapy (HDC) regimens followed by bone marrow transplantation (BMT) are fitted with a central venous catheter which is usually inserted a few days before hospitalisation in the transplantation unit. Usually, central venous catheter dressings are changed, empirically, every 3 or 4 days,[1,2] whatever the state of the dressing and mostly because less frequent changes are suspected of promoting local infections likely to give rise to bacteraemia in granulocytopenic patients. Cutaneous lesions caused by catheter dressing changes are even worse because chemotherapy-induced cutaneous toxicity is high and can generate intense local pain during and between these changes. In addition, skin lesions may increase the risk of cutaneous colonisation and thereby exacerbate the risk of catheter-related sepsis.

The busulfan-thiotepa conditioning regimen used to treat children with brain tumors is associated with particularly severe skin toxicity.[3] These patients develop serious burn-like cutaneous lesions and the weakened skin sticks to the dressing and comes away when it is removed. These reactions and the attendant pain led us to lengthen the interval between catheter dressing changes to 15 days. The good results obtained in terms of attenuated cutaneous toxicity and the apparent absence of infectious complications observed in these patients, prompted further studies to determine whether this approach could be adopted for any HDC regimen. The expected benefit in limiting dressing frequency was a reduction of skin toxicity and thus an improvement in the quality of life of in-patients and reduced costs in terms of nursing time.

A randomised controlled trial was undertaken in children hospitalised in the Paediatric Bone Marrow Transplantation unit at the Gustave Roussy Institute to compare the efficacy of two catheter dressing change frequencies (4 days *vs* 15 days) (1) in preventing skin toxicity at the catheter dressing site and its periphery, (2) in attenuating pain during and between dressing changes, (3) without promoting local and systemic infection.

Patients and methods

Patients

Patients eligible for inclusion were children with a malignancy, who were candidates for HDC and autologous or allogeneic BMT. Patients were only included once in the trial. Patients treated with the busulfan-thiotepa conditioning regimen and patients who already had grade $\geqslant 2$ cutaneous toxicity (see below) at the catheter dressing site were not eligible. A qualitative culture of the skin at the catheter entry site was performed before randomisation; only patients with a negative culture or a *Staphylococcus epidermidis*-positive culture were eligible. Written informed consent was required from parents of all eligible children. This protocol was approved by the ethical committee in Kremlin-Bicêtre, France.

Treatments

Only single lumen silastic catheters (Vygon) were used. Catheters were all inserted (subclavian site) in the operating room under strict aseptic conditions. Physicians wore a cap, a mask, sterile gloves and a gown. The insertion site was first qualitatively cultured and then prepared with 0.5% alcoholic chlorhexidine (Hibidil). The catheters were then inserted cutaneously using the Seldinger technique, and tunnelled subcutaneously up to 10 cm on average in order to allow rapid removal of the material if severe infectious complications were suspected. In the absence of catheter-related adverse events, the device was left in place until the patient was discharged from the BMT unit.

Eligible patients were randomised on the first day of HDC. A computer-generated list was used to allocate patients to the 15-day (15Dy group) or the 4-day (4Dy group) treatment arm. Randomisation was stratified by the type of HDC (with or without busulfan), because this drug is notorious for causing cutaneous toxicity.[4]

To avoid any bias associated with the dressing policy, choice of the type of dressing and of antiseptics used at catheter insertion and at each dressing change was strictly identical in the two treatment groups. The trial results therefore concern the entire strategy, including dressing change frequency and choice of dressings and antiseptics. Based on our previous experience, three types of dressing were used according to cutaneous toxicity; the adhesive transparent oxygen-permeable type (Tegaderm) for grade 0 and 1, the Mefix type for grade 2 and 3 and the sterile gauze and tape (American style) dressing (Surgifix or Velpeau) for grade 4. Dressings were changed by the nurse in charge of the patient, under sterile conditions: the dressing was cautiously unstuck, the skin was cleaned with a sterile gauze and Hibidil from the catheter entry point towards periphery. A sterile gauze was then applied under the dressing. The dressing had to cover the catheter entry point as well as the catheter hub, and the upper limit of the extension line, whatever the dressing type.

According to national recommendations at the time of the trial, antiseptics used for the preparation of the dressing site were Hibidil initially, then Eosine or Betadine when necessary, according to the condition of the skin.

In both groups, if a dressing change had not been planned (soiled or loosened dressing) or if the catheter had to be changed (twisted or plugged catheter, accidentally torn or dislodged catheter), the subsequent dressing had to be placed as stipulated in the initially allocated treatment arm (15 or 4 days later). A guide-wire exchange over an existing catheter was not permitted. When the catheter had to be replaced contralaterally before skin toxicity occurred, the data were censored on the date the catheter position was changed.

When the skin culture at the catheter entry site became positive during follow-up, choice of the subsequent dressing frequency was at the discretion of the investigator. The patient was nonetheless analysed in the initial treatment group according to the 'intent to treat' principle.

Catheters were used to administer parenteral nutrition, blood products, and medication. Parenteral antibiotics were administered prophylactically starting on the day of BMT based on the results of a previous randomised study.[5] Each patient was isolated in a laminar air-flow room. Food was carefully selected and thoroughly cooked to obtain a diet low in viable microbial content. None of the patients received hematopoietic growth factors.

Follow-up

Daily surveillance of the dressing and its periphery began on the day of randomisation and was continued throughout hospitalisation. Whenever the dressing was changed, the grade of skin toxicity was recorded. Given the strong association between microbial growth on the skin at the entry site and the development of canula-related infection,[6–8] a bacteriological sample was obtained from the skin around the catheter entry point, before any cutaneous antisepsis. Blood cultures and catheter entry site cultures were taken in the event of fever above 38.5°C, and/or signs of local infection. The intensity of pain during dressing changes and any pain since the last change were also recorded.

Assessment criteria

The main assessment criterion concerned skin toxicity at the catheter dressing site and at its periphery. The skin status was classified as follows: grade 0: healthy skin, grade 1: slightly inflammed skin, grade 2: minor cutaneous lesions, dressing difficult to remove, grade 3: lesions reaching the periphery of the dressing, grade 4: cutaneous lesions to such an extent that the usual dressing could no longer be used. As dressing changes were performed by many different nurses, the skin toxicity grading scale was tested during the 6 months preceding the trial so that the different nursing teams could familiarise themselves with its use. Skin toxicity (grade $\geqslant 2$), occurring during hospitalisation, was considered a treatment failure.

The other assessment criteria were the incidence of documented bacteraemia analysed sequentially according to a stopping rule (see below) and the degree of local pain (classified as none, moderate or severe) during the dressing change and between dressing changes. As positive cultures at the dressing site are obviously underestimated when

dressings are changed every 15 days, this criterion was not a study endpoint.

Sample size

It was estimated[9] that a minimum of 55 patients per group would be necessary to demonstrate a minimal difference of 30% in the rate of grade $\geqslant 2$ skin toxicity during hospitalisation, (two-tailed test, $\alpha = 5\%$, $\beta = 10\%$, skin toxicity rate previously observed with the standard 4-day rhythm around 30%).

Statistical methods

Analyses were carried out on an intention-to-treat basis. Differences between groups were evaluated by two-sided tests. All analyses concerning assessment criteria were adjusted on the stratification criterion (busulfan yes/no).

In the life table analysis, the date of the first dressing (date of randomisation, or date of the dressing just before randomisation) was used as the starting point and the date of the event studied as the endpoint. The curves were estimated according to the Kaplan–Meier method[10] and carry Rothman's 95% confidence intervals;[11] they were compared by the logrank test.[12]

In our experience, the rate of bacteraemia due to *Staphylococcus epidermidis* observed among grafted children is 5%. Early trial interruption was planned, according to a sequential design[13] in the event of an unacceptable rate (reaching 15%) of bacteraemia due to *Staphylococcus epidermidis* or to any other micro-organism found at the catheter entry site in the 15Dy group.

Microbiological methods

Bacteriological samples were taken from skin around the catheter entry point, using plastic agar-coated slides (Unipath SA, Dardilly, France). All colonies appearing within 48 h of incubation (37°C) were identified by the usual qualitative bacteriological procedures.

Results

Patients entered the trial between July 1990 and April 1993. A total of 113 patients were randomised, 57 in the 15Dy Group and 56 in the 4Dy Group. One patient relapsed after randomisation and did not receive HDC (15Dy Group). The analysis presented here thus concerns 56 patients in each group. Table 1 shows initial patient characteristics and treatment details in the two groups. An initial positive bacteriological sample was found at the catheter entry point in nine patients (five in the 15Dy group and four in the 4Dy group). All nine had been colonised by *Staphylococcus epidermidis*. Patients received combined HDC with (3%) or without (97%) total body irradiation as a conditioning regimen for BMT. A similar proportion of patients in the 15Dy group (48%) and the 4Dy group (46%) had busulfan in their HDC regimen.

Aplasia occurred 8 days (range 1–15) after the start of HDC in both groups and lasted for a similar mean duration: 26 days (s.d. = 13), and 25 days (s.d. = 12), respectively. The mean duration of hospitalisation was 48 days (s.d. = 13) in the 15Dy group and 47 days (s.d. = 19) in the 4Dy group. Among the 112 patients analysed, two died of veno-occlusive disease in the 4Dy group before bone marrow recovery. Both patients had developed cutaneous toxicity before death but there was no evidence of a micro-organism in the culture of the skin at the catheter entry point.

Table 1 Initial characteristics of 15-day (15Dy) and 4-day (4Dy) groups[a]

	15Dy	*4Dy*
No. patients	56	56
Males	59%	45%
Diagnosis		
Neuroblastoma	52%	46%
Rhabdomyosarcoma	11%	9%
Ewing's sarcoma	9%	9%
Lymphoma	5%	14%
Other	23%	22%
Age at graft, median (range) years	5 (1;22)	7 (2;19)
Initial cutaneous grade 1 toxicity	5%	9%
Presence of *Staphylococcus epidermidis* in the initial sample	9%	7%
Skin complexion		
White	77%	84%
Mat	18%	11%
Black	5%	5%
Autologous BMT	93%	95%
Purged marrow	43%	46%
HDC regimen		
With melphalan	41%	34%
With busulfan	48%	46%
Other	11%	20%

[a]No differences between the groups were statistically significant.

Compliance

During hospitalisation, patients experienced a mean of 7 (s.d. = 3) and 12 (s.d. = 5) catheter dressing changes in the 15Dy and 4Dy group, respectively, corresponding to a change every 8 days (s.d. = 4) and every 4 days (s.d. = 1) on average. Table 2 shows the reasons for premature dressing changes among the 1064 dressings performed during the follow-up period (386 in the 15Dy group and 678 in the

Table 2 Reasons for dressing changes

	15Dy n (%)	*4Dy n (%)*	*Total*
Per protocol	67 (17)	516 (76)	583
Detached dressing	175 (45)	50 (7)	225
Soiled dressing	29 (8)	13 (2)	42
Dislodged catheter	1	1	2
Plugged catheter	24 (6)	34 (5)	58
Changed catheter	1	2	3
Twisted catheter	26 (7)	13 (2)	39
Other reason	59 (15)	45 (7)	104
Other side	4 (1)	4 (1)	8
Total	386	678	1064

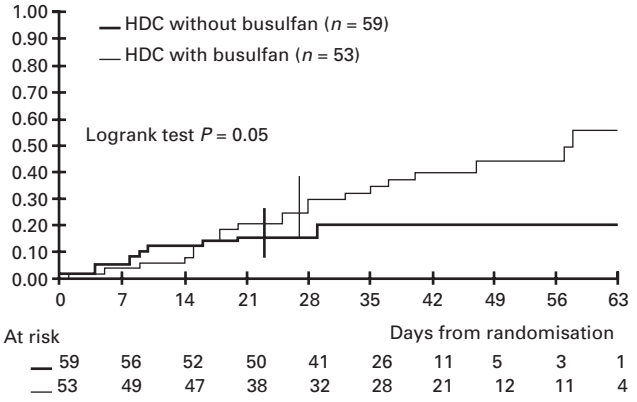

Figure 1 Actuarial proportion (95% confidence interval) of patients with grade ⩾2 local skin toxicity according to the high-dose chemotherapy regimen.

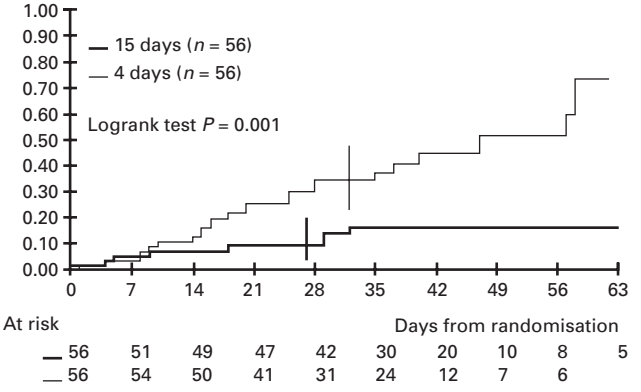

Figure 2 Actuarial proportion (95% confidence interval) of patients with grade ⩾2 local skin toxicity in the two treatment groups.

4Dy group). Only 17% of dressing changes were performed per protocol in the 15Dy group compared to 76% in the 4Dy group ($P < 0.001$). In the 15Dy group, the main reason for an earlier change was a loose dressing (45%).

Cutaneous toxicity

As expected, the rate of skin toxicity during hospitalisation was higher ($P = 0.01$) in patients with busulfan in the HDC regimen (40%) than in other patients (19%). Figure 1 shows the incidence of skin toxicity in the two groups (logrank test $P = 0.05$).

Table 3 shows the maximum cutaneous toxicity grade observed in the two treatment groups. A total of 32 patients had grade 2 or more severe toxicity: eight in the 15Dy group and 24 in the 4Dy group. The cumulative proportions (s.d.) of patients with skin toxicity 2, 4 and 6 weeks after conditioning were 7% (7%), 14% (10%), 16% (11%) in the 15Dy group and 16% (10%), 34% (13%) and 44% (15%) in the 4Dy group (Figure 2, logrank test $P = 0.001$). Patients in the 4Dy group, had a 3.4-fold risk of developing grade ⩾2 toxicity compared to patients in the 15Dy group. When adjusted on the presence of busulfan in the HDC regimen, the significance of the test improved (logrank test $P < 0.001$).

Pain

The maximum intensity of local pain was analysed. The proportion of patients complaining of pain during the dressing change was 32% in the 15Dy group and 48% in the 4Dy group ($P = 0.09$ when adjusted on busulfan). The difference between the proportion of patients with 'severe' pain (5% and 9%, respectively) was not significant. The maximum intensity of local pain ('severe') between dressings was attained in five (9%) patients in the 15Dy group and in 10 patients (18%) in the 4Dy group ($P = 0.18$).

Table 3 Maximum skin toxicity during the follow-up period

	15Dy n (%)	*4Dy n (%)*	
Grade 0	21 (37)	10 (18)	31
Grade 1	27 (48)	22 (39)	49
Grade 2	6 (11)	19 (34)	25
Grade 3	1 (2)	4 (7)	5
Grade 4	1 (2)	1 (2)	2
Total	56	56	112

Infections

No catheters had to be removed during the study because of a suspicion of catheter-related infection. The proportions of patients with one or more positive bacteriological sample(s) at the catheter entry point during hospitalisation were not significantly different (15 (27%) in the 15Dy group and 13 (23%) in the 4Dy group). The micro-organism most often implicated was *Staphylococcus epidermidis* alone (12 and eight patients, respectively) and then *Staphylococcus aureus* (one and two patients, respectively); various other micro-organisms were identified in the other five patients (*Candida albicans, Escherichia coli, Klebsiella* sp., *Actinobacter* sp. and *Stenotrophomonas maltophilia*).

Thirteen cases of bacteraemia were observed during the follow-up period. Six (11%) patients had at least one bacterium in the 15Dy group and 7 in the 4Dy group (13%). In the 15Dy group, the micro-organisms isolated in the blood cultures were: *Staphylococcus epidermidis* (two), *Pseudomonas aeruginosa* (one), *Candida tropicalis* and *Staphylococcus epidermidis* (one), *Klebsiella* sp. and *E. coli* (one) and *Fusobacter* (one). Only one of these episodes of bacteraemia (mixed *Klebsiella* sp. and *E. coli* infection) was related to demonstrated colonisation of skin at the catheter entry site. No primary port of entry could be identified for the other five. In the 4Dy group, the micro-organisms isolated in the blood cultures were *Staphylococcus epidermidis* (three), two of which were polymicrobial, *Enterobacter cloacae* (one), *Stenotrophomonas malto*. (one), *Candida* (one) and *Coli* (one). Of these seven episodes of bacteriaemia, only one was related to demonstrated colonisation of skin at the catheter entry site (*Staphylococcus epidermidis* infection). In conclusion, only one infection in each group was catheter related. All 13 episodes had a favourable out-

come, six requiring prolonged intensive supportive care (two in the 15Dy group and four in the 4Dy group).

Discussion

Skin toxicity often occurs after any kind of HDC combination. This side-effect is usually mentioned in the BMT literature but is not described in detail when toxicity is very severe.[3] In our experience, when all HDC protocols are pooled, approximately 50% of patients develop various degrees of toxicity. The frequency and the intensity of this complication is contingent upon the HDC protocol, and reaches 80% in patients treated with busulfan and thiotepa who develop serious burn-like cutaneous lesions.

Cutaneous lesions worsen at the catheter entry point because dressings are changed frequently. Local lesions can be very painful and can cause tremendous discomfort. The absence of complications observed in our unit as a result of limiting the frequency of dressing changes from 4 to 15 days among patients treated with busulfan-thiotepa prompted us to propose a similarly reduced frequency for all children undergoing HDC followed by BMT. To our knowledge, this study is the first to compare two dressing change rhythms in children treated for cancer with high-dose chemotherapy and bone marrow transplantation.

Given the high rate of skin toxicity attributed to busulfan,[4] randomisation was stratified on the presence of this drug in the HDC regimen and results were adjusted on this factor. Our data clearly confirm the prognostic value of busulfan: skin toxicity was significantly higher ($P = 0.01$) in patients treated with busulfan in the HDC regimen (40%) than in other patients (19%).

The sample from the catheter entry point was initially positive for *Staphylococcus epidermidis* in nine patients and this figure is in accordance with the predominance of *Staphylococcus epidermidis* in the resident skin flora of patients.[14] The proportions of such patients were similar in the two groups and none of them developed bacteraemia.

Skin toxicity (defined as grade $\geqslant 2$) occurring during hospitalisation was considered a treatment failure. As dressing changes are performed by many different nurses, the skin toxicity grading scale was tested during the 6 months preceding the trial to familiarise the different nursing teams with its use.

In the 4Dy group the interval was not respected in 24% of dressing changes. The proportion of dressing change protocol violations in the 15Dy group was 83%, the main reason being that it became unstuck (55%). Our study concerns very young children, 30% of whom were below 4 years of age. The incidence of catheter- or dressing-related problems is probably higher in such young patients[15] than in older patients. We therefore considered it reasonable to propose a mean frequency of 8 days which is now routinely applied in our unit.

Children undergoing HDC followed by BMT are at a very high risk of infection induced by prolonged neutropenia. In this trial, which was conducted before peripheral blood stem cells and granulocyte colony-stimulating factors were widely used, the mean duration of aplasia was 26 days. Such a prolonged duration is also explained by the high proportion of purged marrow candidates (45%) in this trial. Moreover, all such patients require a central venous catheter, a potential risk factor for infection[16–19] in immunocompromised patients.

As positive cultures at the dressing site are obviously underestimated when dressings are changed every 15 days, this criterion was not a study endpoint. One or more positive bacteriological sample(s) was found in 25% of patients, at the catheter entry point, and 12% developed documented bacteraemia. These rates are relatively low[6,15] due to the stringent hygiene conditions in the rooms, the diet given in the transplantation unit and the use of early prophylactic antibiotherapy. These rates were similar in both groups and show that less frequent dressing changing is not a risk factor for local or systemic infections, provided aseptic conditions are respected. On the contrary, less frequent dressing changes could be an efficient means of reducing the risk of skin colonisation by limiting the likelihood of skin erosions and thus the adherence of micro-organisms. In three cases, *Staphylococcus epidermidis* was responsible for bacteraemia but the same micro-organism was found at the catheter entry site in only one case (4Dy group). It is now well established that negative skin cultures are highly sensitive for ruling out catheter infection, but the positive predictive value of such a test is below 62%.[8] In the two cases in which *Staphylococcus epidermidis* was implicated in cutaneous colonisation, bacteraemia could have been due to intraluminal catheter colonisation, or this micro-organism may have originated from other sources of infection.[20]

As different dressings and antiseptics were used according to the grade of cutaneous toxicity, the lower rate of infection in the 15Dy group could be considered due to greater usage of more effective antiseptics. However, this point does not have an impact on the present findings since the trial results concern the entire strategy, including dressing change frequency and choice of dressings and antiseptics.

To our knowledge, this is the first study to compare two dressing change intervals in paediatric cancer treatment. In their study comparing two dressing change intervals (once or twice a week) in 32 adult neutropenic haematological patients, Engervall *et al*[21] found no significant difference in central venous catheter-related infections or in the duration of erythema in the 'once-a-week group'. However, they found a higher rate of positive catheter tip cultures, and a tendency towards more Gram-positive bacteraemia in the 'once-a-week group'. They therefore recommended changing dressings twice a week. However, their recommendations are not firmly supported by their data, and their study, which involved a low number of patients, was not performed in an intensive care unit and exclusively concerned adults.

The analysis of pain is difficult to interpret because several contributing factors other than dressings may play a role and because pain is associated with the type of dressing which is itself selected according to the grade of skin toxicity. Nevertheless, the proportion of patients who complained of pain during the dressing change was lower (32%) in the 15Dy group than in the 4Dy group (48%), albeit not significantly ($P = 0.09$). However, given the multiplicity of aggressive medical tests, examinations and treatments these

children have to undergo, limiting catheter dressing changes probably contributes to a gain in quality of life, which is far from negligible.

The mean number of dressing changes during hospitalisation was 7 (s.d. = 3) in the 15Dy group and 12 (s.d. = 5) in the 4Dy group. As the mean amount of time required to reapply a dressing is about 15 min, a decrease of this magnitude is extremely cost-effective in intensive care units where the nursing workload is considerable.

In conclusion, the main result of this trial is a 70% relative reduction in the incidence of local skin toxicity in the group with less frequent dressing changes. Limiting the frequency of dressing changes did not increase local infection and the rate of catheter-related bacteraemia. The planned 15-day frequency could not be maintained. An 8-day frequency has been used since the end of the trial in our transplantation unit and has proved effective since infection rates have not increased. Based on this practical experience, we can legitimately recommend this catheter dressing change strategy as a standard procedure in haematolological intensive care units where patients are subject to rigorous measures of asepsis. By demonstrating that limiting dressing change frequency results in a lower rate of skin toxicity, this trial provides original results both in terms of quality of life of in-patients and reduction in the workload of the nursing personnel. However, it should be emphasised that this frequency has been demonstrated to be efficient in an haematological intensive care unit. The safety of this procedure must be confirmed before its extension to medical or surgical intensive care units.[22,23]

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