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Original Article

Nursing Management of Haemorrhagic Cystitis in Patients Undergoing Haematopoietic Stem Cell Transplantation: a Multicentre Italian Survey

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Abstract. ***Background:*** **Haemorrhagic cystitis (HC) is a severe complication occurring after haematopoietic stem cell transplantation (HSCT) in 13-40% of patients, caused by infectious and/or non-infectious factors that increase the in-hospital length of stay and the risk of mortality of transplanted recipients. Although different management interventions have been suggested in the literature, available knowledge on interventions performed by Italian nurses in their daily practices has not been documented to date.**
Aim of the study: **The aim of this study is to describe HC preventive and treatment interventions in patients undergoing HSCT as performed by Italian nurses in their daily practice.**
Material and methods: **A multicentre survey was conducted in 2018 by inviting all 110 Italian HSCT centres belonging to the Italian Group for Bone Marrow Transplantation (GITMO). Data collection was performed with an online questionnaire submitted to GITMO reference nurses working in each HSCT centre. Descriptive statistics were performed.**
Results**: A total of 38 Italian centres participated. The preventive intervention most applied in daily care was the mesna administration (n=37; 97.4%), followed by intravenous hyperhydration (n=33; 86.8%) and forced diuresis with furosemide (n=24; 63.1%). Preventive continuous bladder irrigation (CBI) was performed in 13 centres (34.2%). Transfusions of blood products (n=32; 84.2%), CBI (n=31; 81.6%) and intravenous hydration (n=28; 73.7%) were the most applied treatments, beyond the administration of analgesics (n=38; 100.0%) and antispasmodics (n=26; 68.4%).**
Conclusion: **A great variability both in the HC prevention and treatment interventions applied in daily practice across centres have emerged suggesting that no strong recommendations in the field are available to date. Therefore, there is a need to increase the evidence available in the field by providing methodological studies of higher quality, multicentre and prospective.**

Keywords: Haematopoietic stem cell transplantation; Haemorrhagic cystitis; Italy; Management; Nursing; Prevention; Professional experience; Supportive measures; Survey; Treatment.

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Introduction. In patients undergoing haematopoietic stem cell transplantation (HSCT), haemorrhagic

cystitis (HC) is a severe complication with an estimated incidence of 13% to 40%.[1–4] Infectious and/or non-infectious factors contribute to HC occurrences, such as adenovirus (ADV) or BK polyomavirus (BKPyV) reactivation,[5,6] conditioning regimens,[4,7] graft-versus-host disease (GVHD),[2,8] and the stem cell sources or donor-recipient incompatibility.[1,9] HC is responsible for the bleeding from the bladder mucosa and a widespread symptomatology including burning, bladder pain, and severe haematuria with clots retention with possible renal failure.[10] HC has been classified as early-onset (EOHC) when it occurs within 48 hours after the conditioning regimens, or late-onset (LOHC) when it occurs after 48 hours.[11] Moreover, HC has been documented to increase the in-hospital length of stay and the risk of mortality.[3,6]

As emerged from a recent scoping review,[12] urine alkalinisation, hyperhydration and forced diuresis have been the most recommended preventive HC measures;[1,2] however, conflicting data have been reported regarding the effectiveness of the preventive application of the continuous bladder irrigation (CBI).[1,2,13] The agent 2-mercaptoethanol sodium sulphonate (mesna) has been documented to reduce the urothelial exposure to chemotherapy, particularly cyclophosphamide.[1,2,13] Even ciprofloxacin as a prophylactic measure has been reported to be effective in reducing the incidence of severe BKPyV-associated haemorrhagic cystitis (BKPyV-HC).[14]

Regarding the HC treatment, no gold standard has been established to date; however, cidofovir (CDV) seems to be the most effective against BKPyV-HC.[15–18] Mackey (2012)[19] has demonstrated the use of intravesical CDV as capable of limiting the risk of renal damage, compared to its intravenous administration. Other promising antivirals against ADV or cytomegalovirus (CMV)-associated HC have also been documented.[18,20] Moreover, in cases of refractory HC, the administration of intravesical prostaglandins has been suggested[21,22] in addition to local therapies, e.g., formalin and alum,[23] hyaluronic acid,[24] and fibrin glue.[25] Furthermore, recent studies have suggested the administration of specific T-BKPyV cells as a new therapeutic option to treat HC and to minimise the risks of GVHD,[26,27] while cystoscopies, cauterisations and surgical interventions have been found as useful in severe grades of HC or life-threatening conditions.[21,28] Supportive measures such as CBI, analgesics and blood products have also been suggested.[15,19,21,22,28] However, which preventive or treatments are daily performed at the bedside have been rarely documented. Cesaro, on behalf of the ECIL-6 working group (2018),[29] has recently updated the Guidelines for the Management of BKPyV-associated HC in HSCT recipients; nevertheless, no recommendation above grade C (=marginal support for use) has been established in the field of HC treatment.

To date, only three surveys[30,31,32] have been published on this subject. Gargiulo et al. (2014)[32] in their prospective study among 30 Italian HSCT centres reported an overview of interventions applied by Italian nurses and physicians in paediatric and adult transplanted patients. As reported by the involved experienced professionals, quinolones (87.3%) followed by hyperhydration (85.3%) and urine alkalinisation (62.2%) were the most common preventive interventions, while the bladder catheter insertion was reported by 11.8% of the centres. Among treatments, hyperhydration (56.3%), bladder catheter placement (56.3%), CBI (27.2%) and CDV (12.7%) were the most applied. The survey conducted in 2016 by Schneidewind et al. (2017)[31] was addressed to haematologists and urologists among the European Bone Marrow Transplantation (EBMT) centres in Germany, focusing on the management of BKPyV-associated HC in the adult population by using a questionnaire. According to the findings, local bladder therapy was the most effective treatment in the opinion of 63.3% of haematologists, followed by CDV medication (26.7%) and other therapies (10.0%). Urologists mainly reported the use of CBI (92.6%) and local therapies (27.8%, as cidofovir, leflunomide, tranexamic acid and alum), while systemic therapy was applied less often (14.8%). More recently, Cesaro and colleagues (2018)[30] performed a survey on ADV infections management in Europe, Russia and the Middle East among 89 EBMT centres. CDV was the medication most applied. The reduction of immunosuppression (84%) and the administration of brincidofovir (27%) were largely adopted, especially among the paediatric population to treat ADV infection.

With the intent to advance the available knowledge on prevention and treatment as performed in their daily practices, the principal aim of this study was to describe interventions of Italian clinical nurses to prevent and manage HC. A secondary aim was to describe the professional experience of nurses in managing HC as well as their perceived HC effects on patients.

Materials and Methods. A national-wide online survey was performed in 2018 involving the Italian Group for Bone Marrow Transplantation (GITMO) network. Eligible participants were clinical nurses who at the time of the survey: (a) were members of GITMO, (b) were active clinical nurses in one of the Italian HSCT centres included in the GITMO network, and (c) were willing to participate in the survey. A total of 110 clinical nurses were found eligible.

Data collection. A questionnaire was developed by researchers in cooperation with the GITMO nurses' board members and piloted by five clinical nurses not

involved in this final survey. After the piloting, no changes were required. In the questionnaire were included all interventions documented in the literature which were aimed at preventing and managing HC, as emerged from a scoping review.[12] The final version of the anonymous online survey was based upon 22 items divided into the following four sections:

(1) Section 1: exploring the main demographic characteristics of responding nurses, as well as the number of HC cases they recalled to have managed in 2017, by using closed (n = 3), multiple choice (n = 2) and short open-answer questions (8 items),
(2) Sections 2 and 3: assessing preventive and treatment interventions as performed in daily practice using multiple-choice questions (n = 3); open questions (n = 2) were set regarding timing and specification of the interventions applied (e.g., administration routes),
(3) Section 4: exploring nurses' experiences while managing patients with HC (n = 3) regarding (i) the encountered difficulties, (ii) the perceived impact of HC on patients and (iii) on the nurses, by using 5-degree Likert scales (e.g., 1 = no impact, 5 = maximum impact). Area of investigation and items for each area have been established based on the available literature[12] and the available data from the GITMO network, where previous research in the field has been conducted.

Nurses were left free to fill in the questionnaire with the support of physicians; only 12 (31.6%) filled in the questionnaire autonomously, while the remaining 26 (68.4%) had the cooperation of a physician working in the same centre, as emerged from the last question of the questionnaire.

A presentation letter reporting the aims of the study, as well as access instructions and the questionnaire link, was sent to all GITMO network centres. The completion of the questionnaire was intended as the consent to participate in the survey. Two reminders were performed by e-mail and by phone to promote responses. All procedures were in accordance with the ethical standards of the GITMO and with the 1964 Helsinki Declaration.

Data Analysis. The answers were reported and analysed with Microsoft Excel 2013 and then processed with the SPSS V 24.00. Descriptive statistics were performed (frequencies, percentages, means, standard deviations [SD, ±], confidence intervals [CIs] at 95%). Open answers were read by two researchers and then summarised according to their commonalities and differences.

Results. A total of 38 clinical nurses participated, mainly caring for adult patients (24; 63.1%). Of the 110 centres, 34.5% were represented. Most of the participants were female (29; 76.3%) with an average age of 46.3 ± 8.4 years. The majority of them were educated at the university level (20; 52.6%), and at the time of the study had been working an average of 15.8 ± 8.3 years, as reported in **table 1**.

Table 1. Sociodemographic characteristics of participant nurses and HSCT centres (=38).

Clinical Nurses	**N = 38 (%)**
Gender	
Female	29 (76.3)
Age of nurses (years), mean (SD; CI 95%)	46.3 (8.4; 43.5–49.0)
Education	
Bachelor's degree	20 (52.6)
Diploma of nursing	18 (47.4)
Working years as nurse in the HSCT centre, mean (SD; CI 95%)	15.8 (8.3; 13.0–18.5)
HSCT centre, mission	
Adult	24 (63.2)
Paediatric	8 (21.0)
Adult and paediatric	6 (15.8)
Transplants performed in HSCT centres*, total	2,361
Transplants performed in each HSCT centre*, mean (SD; CI 95%)	62.1 (37.2; 49.7–74.4)

Legend: CI: confidence interval; HSCT: haematopoietic stem cell transplantation; N: number; SD: standard deviation.
*according to the data reported by nurses in the questionnaire; referred to year 2017.

According to that recalled by participants, an average of 62.1 ± 37.2 (range 14–185) transplants were performed in 2017. The median number of HC cases in the same reference year was 2.4 ± 2.7 (CI 95% 1.5–3.2), leading to a prevalence rate of 3.8% as reported in **table 2.** The HC cause recalled by clinical nurses was mainly infectious (19; 65.5%), such as BK virus (15; 51.7%). The recalled onset after HSCT was on average 25.0 ± 27.7 days (ranging from 3–180) and the HC duration was 23.7 ± 23.35 days (ranging from 5–150). The grading of the common terminology criteria (CTC) of the National Cancer Institute (NCI)[33] was the most used assessment tool for HC (22; 57.9%). In 52.6% of centres (n = 20), there were protocols or checklists guiding nursing care interventions, as reported in **table 2**.

Preventive interventions. In order to prevent HC, the most applied intervention reported by nurses was the intravenous mesna (37 of 38 centres; 97.4%), followed by hyperhydration with normal saline solution (33; 86.8%) and forced diuresis with furosemide (24; 63.1%). The placement of a three-way urinary catheter to supply CBI was carried out in 13 centres (34.2%). The least applied preventive intervention was the oral hydration and the placement of the bladder catheter, as reported in **table 3**. Several centres (10; 26.3%) applied four preventive interventions per patient, whereas 1

Table 2. HC data in the involved Italian HSCT centres (=38).

Epidemiological data on HC	**N = 38 (%)**
Cases of HC*	90
Cases of HC*, mean (SD; CI 95%)	2.4 (2.7; 1.5–3.2)
HC grading tool used in daily practice	
NCI CTCAE (2017)[33]	22 (57.9)
Bedi et al. (1995)[34]	4 (10.5)
Sencer et al. (1993)[44]	1 (2.6)
Bearman et al. (1988)[45]	1 (2.6)
Droller et al. (1982)[35]	2 (5.3)
None	8 (21.0)
Main aetiology of HC*	**N = 29 (%)**
Infectious	19 (65.5)
Related to conditioning regimen and infections	3 (10.3)
Related to the conditioning regimen	2 (6.9)
Acute GVHD	2 (6.9)
Idiopathic	1 (3.4)
Related to conditioning regimen and acute GVHD	1 (3.4)
Non-identifiable, multifactorial	1 (3.4)
Specific aetiology of HC*	
BKV	15 (51.7)
CY+BKV	4 (13.8)
CY	1 (3.4)
CY-BU	1 (3.4)
BKV+ADV	2 (6.9)
BKV+JCV	1 (3.4)
BKV+ADV+JCV	1 (3.4)
CY-BU-FLU+BKV	1 (3.4)
CY+BKV+TBI	1 (3.4)
Unspecified	2 (6.9)
Estimated onset of HC (days from HSCT), mean (SD; CI 95%)	25.0 (27.7; 15.9–34.1)
Estimated duration of HC (days), mean (SD; CI 95%)	23.7 (23.3; 16.1–31.4)
HC management protocol available at the unit level, yeas	**20 (52.6)**

Legend: ADV: adenovirus; BKV: BK virus; BU: busulfan; CI: confidence interval; CY: cyclophosphamide; FLU: fludarabine; GVHD: graft versus host disease; JCV: JC virus; HC: haemorrhagic cystitis; HSCT: haematopoietic stem cell transplantation; N: number; SD: standard deviation; TBI: total body irradiation.
*according to the data reported by nurses in the questionnaire; referred to year 2017.

(2.6%), 4 (10.5%), 8 (21.0%), 6 (15.8%), 6 (15.8%) and 3 (7.9%) centres have applied one, two, three, five, six and seven interventions per patient, respectively. Intravenous mesna administration was usually started at the beginning of cyclophosphamide (CY) administration in more than half of the centres (25 of 37; 67.6%); five centres specified "at the beginning of the conditioning regimen." The administration ended

Table 3. HC preventive and treatment interventions as applied by nurses in Italian HSCT centres (=38).

Interventions	**N = 38 (%)**
Preventive interventions	
Intravenous mesna[a]	37 (97.4)
Intravenous hyperhydration with normal saline solution[a]	33 (86.8)
Forced diuresis with furosemide (for diuresis contraction or weight increase > 1 kg)[a]	24 (63.1)
Urine alkalinisation with sodium bicarbonate[a]	20 (52.6)
Three-way intravesical catheter placement and CBI[a]	13 (34.2)
Intravenous hyperhydration with dextrose 5% solution[a]	12 (31.6)
Intravenous ganciclovir[a]	8 (21.0)
Forced diuresis with frequent voiding	5 (13.1)
Urine alkalinisation with acetazolamide[a]	5 (13.1)
Oral hyperhydration	1 (2.6)
Other: intravesical catheter placement for incontinence or difficulty in emptying the bladder in patients with multiple sclerosis	1 (2.6)
Other: intravesical catheter emptying during treatment with cyclophosphamide	1 (2.6)
Treatment interventions	
Blood products transfusions[a]	32 (84.2)
3-way bladder catheter placement and CBI	31 (81.6)
Intravenous hyperhydration[a]	28 (73.7)
Intravenous antivirals[a]	27 (71.0)
Manual irrigation and removal of the clots	27 (71.0)
Oral medications[a]	13 (34.2)
Intravenous medications[a]	12 (31.6)
Oral antivirals[a]	11 (28.9)
Uricosurics[a]	10 (26.3)
Medications through intravesical instillation[a]	9 (23.7)
Collaborating/assisting during evacuative cystoscopies	9 (23.7)
+ application of local therapies	6 (15.8)
+ cauterizations	3 (7.9)
Interruption of the intravesical catheter's outgoing flow after intravesical medications	7 (18.4)
Collaborating/assisting during hyperbaric oxygen therapy sessions	3 (7.9)
Target therapies[a]	2 (5.3)
Antivirals through intravesical instillation[a]	2 (5.3)
Changing patient's position after administration of intravesical medications	1 (2.6)
Oral hyperhydration	0 (-)
Phytotherapeutics	0 (-)

Legend: CBI: continuous bladder irrigation; HC: haemorrhagic cystitis; HSCT: haematopoietic stem cell transplantation; N: number.
[a]under physician's prescription.

at the time of the CY administration (4 of 37; 10.8%) and the conditioning regimen in general (3 of 37; 8.1%), or from 6–48 hours after the last dose of CY (17 of 37; 45.9%); however, 11 (29.7%) centres did not

respond.

Hyperhydration with normal saline was started from the patient admission in the centre to 6 hours before the conditioning (10 of 33; 30.3%), or from the beginning of the conditioning regimen (11 of 33; 33.3%); three participants specified "at the beginning of CY administration". It continued until the end of chemotherapy administration in 8 of 33 centres (24.2%). However, 10 (30.3%) and 14 (42.4%) of 33 centres using hyperhydration with normal saline did not respond regarding when this preventive measure is used to be started and ended, respectively.

Forced diuresis with furosemide was usually started at the beginning of the conditioning regimen in 6 of 24 centres (25.0%)—three participants specified "at the beginning of CY administration"—or at the end of the conditioning (2 of 24; 8.3%). The administration of furosemide usually ended when the conditioning regimen also ended (3 of 24; 12.5%), specifically from 24–48 hours later (4 of 24; 16.7%). However, also, in this case, 14 (58.3%) and 15 (62.5%) centres did not respond regarding when this preventive measure is used to be started and ended, respectively.

Treatment interventions. As shown in **table 3**, the most applied HC treatment is the transfusion of blood products (32; 84.2%), followed by CBI (31; 81.6%) and the intravenous hyperhydration (28; 73.7%). Manual irrigation and administration of intravenous antivirals were reported by 27 centres (71.0%). No centres reported the use of oral hyperhydration and phytotherapeutics. Several centres applied six or seven interventions on the same patient (12 of 38; 31.6%). Among transfused blood components, platelets (24 of 32; 75.0%), packed red blood cells (13 of 32; 40.6%), fresh frozen plasma (5 of 32; 15.6%) and albumin (1 of 32; 3.1%) were reported as being used most often. Most centres, to manually irrigate and remove clots, used a 50–60 mL syringe by injecting a normal saline solution (7 of 27; 25.9%), water for injectable preparations (3 of 27; 11.1%) or distilled water (1 of 27; 3.7%). However, 16 centres (59.2%) did not specify the solution used.

Concerning the CBI, most centres reported using as infusing solution the normal saline (10 of 31; 32.2%) or water for injectable solutions (3 of 31; 9.7%). One centre out of 31 (3.2%) administered CBI using a volumetric pump, and 3 (9.7%) reported using solutions prepared at a lower temperature than that of the environment. Moreover, three centres of 31 (9.7%) started the administration at the onset of microhematuria or large clots, while one centre (3.2%) reported stopping it at haematuria's resolution. Other centres did not report data regarding the timing of CBI use.

The infused solutions for hyperhydration were reported as containing normal saline (15 of 28; 53.6%), sodium bicarbonate (4 of 28; 14.3%) and dextrose 5% (2 of 28; 7.1%). Two centres specified "dextrose 5% with potassium chloride corrections" and "electrolysing rehydrating solutions", respectively.

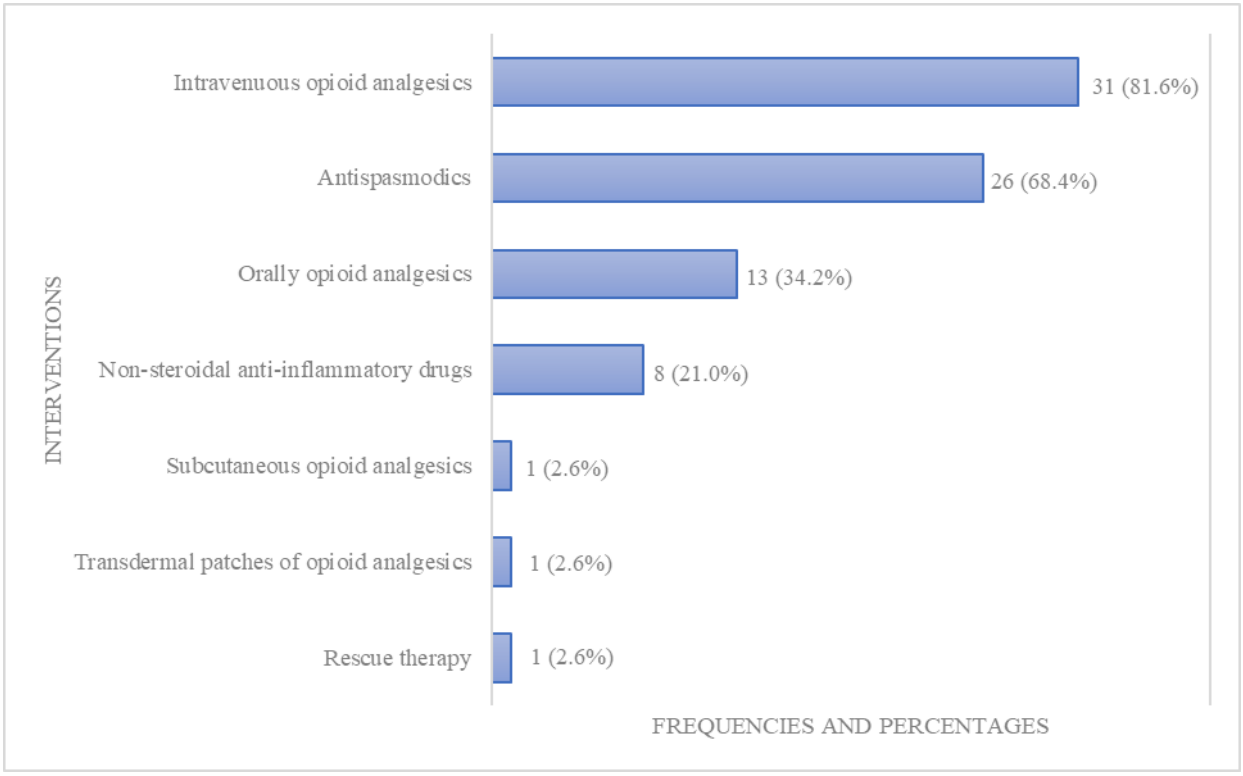
As antivirals, oral acyclovir (5 of 11; 45.4%), oral CDV (11 of 27; 40.7%), intravenous ganciclovir (6 of 27; 22.2%), intravenous foscavir (9 of 27; 33.3%) and intravenous acyclovir (3 of 27; 11.1%) emerged as highly used. CDV was given by intravesical instillation (2 of 38; 5.3%), interrupting the outflow from the bladder catheter for 30 minutes in 3 of 7 centres (42.8%) after the end of the instillation. Among other medications, ciprofloxacin (8 of 13; 61.5%) and levofloxacin, oxybutynin, leflunomide, meropenem, ceftazidime (5 of 13; 38.5%) were reported as used by oral administration. Among those nurses who reported to have supported physicians in evacuative cystoscopies (9 of 38; 23.7%), 3 of them (33.3%) have applied local fibrin glue while one has applied the hyaluronic acid (out of 9; 11.1%) and two the platelet gel (out of 9; 22.2%), respectively. Moreover, three nurses (7.9%) reported having supported clinicians in performing cauterisations.

Figure 1 shows the medications usually given by nurses to relieve pain. The administration of intravenous opioid analgesics (31; 81.6%) and of antispasmodics by prescription (26; 68.4%) were the most applied medications.

Nurses' experiences. As seen in **table 4**, the greatest difficulty that nurses encountered in the management of patients with HC was the large degree of support that these patients required to improve their adverse emotional state due to this complication (average 3.31 out of 5; SD 1.16). The lowest difficulty was the technical management of urinary devices (1.97 out of 5; SD 0.97). According to the experience of nurses, the highest impact of HC is at the patient level, affecting the quality of life (QoL) (4.60 out of 5; SD 0.59). The impact on healthcare professional workloads and processes was the least (3.50 out of 5; SD 1.06). A sense of impotence (2.74 out of 5; SD 1.20), frustration (2.58 out of 5; SD 1.48), dissatisfaction (2.47 out of 5; SD 1.37) and anxiety (2.26 out of 5; SD 1.29) were the most-perceived impacts upon nurses while managing a patient with HC.

Discussion. To the best of our knowledge, this is the first survey at the national level that included nurses and explored the HC preventive and treatment interventions as performed in daily practice. The majority of them completed the questionnaire with physicians, suggesting that in these settings, multidisciplinary care is fundamental. Although higher than that reported in the EBMT Survey on ADV (20%),[30] the response rate was low (34.5%) as compared to that reported by a German survey

Figure 1. Applied interventions to relieve HC-associated pain by Italian nurses in HSCT centres (n =38).



Legend: HC: haemorrhagic cystitis; HSCT: haematopoietic stem cell transplantation; n: number.

Table 4. Professional experiences of Italian nurses while managing a patient with HC (n=38).

Investigated items	Average, SD
Encountered difficulties while caring for a patient with HC (*)	
Supporting the patient with the intent to improve his/her psycho-emotional condition	3.31 (1.16)
Managing pain and HC-related symptoms	2.71 (1.31)
Treating HC	2.66 (1.17)
Managing the functional dependence of patients (e.g., bedridden)	2.42 (0.98)
Technically managing urinary devices (bladder catheter, hand irrigation, instillations)	1.97 (0.97)
Perceived impact of HC on outcomes (**)	
Patients' quality of life	4.60 (0.59)
Psycho-emotional burden of patients	4.47 (0.69)
Psycho-emotional burden of the family	4.29 (0.93)
Nurses workloads	4.00 (0.90)
Healthcare professional workloads and processes	3.50 (1.06)
Agreement/disagreement on provided statements (***)	
"I feel a sense of impotence related to the limited availability of effective interventions"	2.74 (1.20)
"I feel a sense of frustration while managing HC"	2.58 (1.48)
"I am dissatisfied with HC management outcomes"	2.47 (1.37)
"I feel anxiety with regard to possible evolution of HC"	2.26 (1.29)

Legend: HC: haemorrhagic cystitis; n: number; SD: standard deviation.
(*) 1 = no difficulty, 5 = extreme difficulty.
(**) 1 = no impact, 5 = maximum impact.
(***) 1 = completely disagree, 5 = completely agree.

(>70%).[31]

The prevalence of HC was estimated on the basis of the recall of participants – as well as for the HC onset, the duration and the aetiology. Prevalence was around 3.8%, lower than that reported in the literature (19.0%,[1] 12.2%,[32] 32.5%[2]). However, the centres were performing both autologous and allogeneic HSCTs. Autologous HSCTs have been less associated with the risk of developing HC as compared to allogeneic ones.[1,13] The large variability reported regarding the onset of HC after HSCT, and its duration, have been documented as heterogeneous also in the literature.[31,32,34] However, although data collected were reported by nurses with long professional experience (>15 years, thus experts in the field), this may not reflect the actual data of the centres.

The most described HC aetiology is related to infections (specifically to BKPyV). This could be attributed to the advances in prophylaxis against the urotoxic effects with the conditioning regimens and to the more known role of BKPyV and other viruses as risk factors as documented in the recent literature mainly focused upon the viral HCs.[6,15,19,31] The role of busulfan-cyclophosphamide as a risk factor for HC was not confirmed by the multivariate analysis of Tsuboi et al. (2003).[4]

The CTC of NCI[33] in its many versions has been the most applied assessment tool in the haematological centres involved, and several authors[21,26] used this classification. However, Gargiulo et al. (2014)[32] used the score developed by Droller and colleagues (1982),[35]

which was adopted by only two centres in our survey. Increasing comparability of the data in future multicentre studies by applying a common assessment tool is recommended.

Preventive interventions. The most applied preventive intervention is the administration of mesna as reported by several studies.[1,2,13] Its administration is more common compared to Gargiulo and colleagues' data (2014),[32] where mesna was administered in 50.6% of patients. However, fluoroquinolones that Gargiulo et al. (2014)[32] reported as the most applied intervention were not administered in our survey. Rather, the use of quinolones such as ciprofloxacin (8; 21.0%) and levofloxacin (1; 2.63%) has been considered as therapeutic measures. After Leung et al. (2005),[36] Miller et al. (2011)[14] administered ciprofloxacin 500 mg orally every 12 hours until 60 days after HSCT in 44 patients (48 patients did not receive prophylaxis) showing a cumulative incidence of HC of 2.6% in the ciprofloxacin group as compared to 20.9% in the non-treated group (P=0.01). Thus, they demonstrated that ciprofloxacin was effective in reducing the incidence of severe BKPyV-HC.

From the 37 centres administering mesna, some centres preferred intermittent intravenous boluses and some preferred continuous infusion. From the scoping review by Visintini et al. (2019),[12] mesna can be administered by intermittent boluses[2,34] or by continuous infusion.[13] Large variability of practices exists concerning when the mesna should be started and ended. Conflicting data has also emerged, thus causing uncertainty and the absence of standard care plans. Hadjibabaie et al. (2008)[2] administered mesna before CY infusion and every 6 hours for a total of three doses and Vose et al. (1993)[13] tested mesna administration from 1 hour before CY, by continuous infusion, until 24 hours after the last CY dose. Bedi et al. (1995)[34] conducted a randomised controlled trial among 147 American HSCT recipients with HC. Their regimen consisted of 5 intravenous doses at 30 min before CY and 3, 6, 9 and 12 hours after each dose of CY.

As the second- and third-most applied preventive interventions, hyperhydration with normal saline and forced diuresis with furosemide have both been recommended for the prevention of HC.[34] An administration speed of 250 mL/h was used in the randomised controlled trial by Vose et al. (1993),[13] while 2500 mL/day emerged from the retrospective analysis of Gonella et al. (2015).[1] Bedi and colleagues (1995)[34] preferred 2 mL/kg/h until 24 hours after the last CY dose. Dextrose water and normal saline containing potassium chloride have also been utilised.[2] According to our data, only one Italian centre reported the use of oral hyperhydration, a natural way to intake fluids but probably more uncomfortable for patients, considering the quantity of daily water to drink (at least 2 L). In addition, forced diuresis with furosemide was tested by Bedi et al. (1995)[34] as compared to mesna and findings showed equally preventive effectiveness of both interventions (P=0.41). Forced diuresis through frequent voiding has not been documented by studies available as effective in reducing HC as compared to CBI.[37,38]

Data about the effectiveness of preventive CBI are still conflicting.[1,2,13] However, 13 centres have reported using it in daily care. Gonella et al. (2015)[1] suggested considering the benefits and harms of preventive catheterisation and CBI, especially concerning patients' discomfort and an increased risk of urinary tract infections. Moreover, according to the recent ECIL 6 Guidelines (2018)[29] the prophylaxis of BKPyV-HC relying on hyperhydration and bladder irrigation, in particular when using myeloablative conditioning based on CY or other alkylating agents, have been suggested with low levels of evidence and strength of recommendations (hyperhydration=BII, level of evidence from at least one well-designed clinical trial, moderately recommended for use; bladder irrigation; CII=level of evidence from at least one well-designed clinical trial without randomization, marginally recommended for use). Furthermore, the use of specific antivirals and fluoroquinolones have not been recommended (DII).

Treatment interventions. The administration of blood products has been the most applied treatment for HC. Actually, it is considered a supportive treatment, able to improve HC but not effective alone in its resolution.[15,21,34,38,39] However, blood transfusions could be supportive not only for HC but even for the myeloablative effects of chemotherapies, and their common use can be considered a standard of care in patients undergoing HSCT. Bladder catheter placement and CBI have emerged as being widely used. Gargiulo et al. (2014)[32] divided the catheter placement (56.3%) from the CBI (27.2%), and therefore our data could not be compared. Only one centre reported using a 3-way bladder catheter. However, the documented effectiveness of CBI[1,15,40] has been studied in association with other interventions such as the instillation of hyaluronic acid.[24]

Local therapies have been reported as the most up-to-date therapeutic measures by urologists (92.6%) and haematologists (63.3%).[31] From our survey, the administration of intravesical antivirals was reported by only 2 centres using CDV, while 7 reported instillations of hyaluronic acid. Local treatments have been used rarely in Italy until 2014 (CDV instillation, 3.6%; hyaluronic acid instillation, 5.5%).[32] However, intravesical CDV might be an option for symptomatic improvement in patients with BKPyV-HC, without systemic adverse effects such as renal failure.[19]

Furthermore, 7 centres (18.4%) reported interrupting the catheter's outgoing flow at the end of intravesical instillation while 3 interrupted it for 30 minutes (less than the hour suggested in the literature).[21,39] Moreover, among the nine centres implementing evacuative cystoscopies, around one-third of them applied topical fibrin glue at the same time. This measure has been studied mainly in Italy: In the pilot study performed by Tirindelli and colleagues (2009),[25] five patients with refractory HC were treated with fibrin glue through an endoscopic applicator. The treatment showed a positive response in three patients suggesting that fibrin glue may be an effective solution for refractory HC.

Multiple treatments such as intravenous tranexamic acid, immunoglobulins, fibrinogen and antithrombin III have also been used. According to the literature available, CDV—the most frequently reported intravenous antiviral—appeared to have the highest level of activity against BKPyV-HC.[6,15,16,19] However, the recent ECIL 6 Guidelines attributed the highest level of evidence (II= evidence from uncontrolled trials) for CDV that is still recommended as grade C (=marginal support for use), due to its uncertainty ineffectiveness and best dose schedule.[29] Furthermore, the access to CDV has been limited in recent years according to the rules of importation of the medication from abroad and this has certainly influenced its adoption across Italian centres.

In addition to CDV, leflunomide and other therapies such as ciprofloxacin and intravenous immunoglobulins have been studied by haematologists.[31] The use of the antivirals ganciclovir and foscavir, as described in our study, has also been documented in the literature.[18] The role of tranexamic acid as a haemostatic agent was associated with a high risk of thromboembolic events, and it is contraindicated in the management of HC.[41] In our survey, 21.0% of centres reported its administration suggesting the need to improve knowledge on its negative effects among clinicians through educational initiatives. Immunoglobulins, however, appeared safe and effective in association with intravesical prostaglandin E2.[22] These findings reveal a wide range of therapeutic tools with no strong recommendations to guide the clinical practice.

Regarding the manual irrigation and removal of the clots, a procedure which has been largely reported to be used by our centres, only one study based upon a randomised controlled trial[21] reported to have handily removed the clots before carboprost instillation. No data emerged from the German survey,[31] likely because it was addressed to physicians, and this measure is performed by nurses.

Among supportive measures, Ippoliti et al. (1995)[21] and Laszlo et al. (1995)[22] administered analgesics and antispasmodics to reduce the discomfort and pain associated with catheter and intravesical instillations. Patients were premedicated with oral oxybutynin with or without belladonna (a phytotherapeutic) and opium suppositories.[21] These interventions confirm the trend of our survey: intravenous opioid analgesics and antispasmodics were the most used in the daily practice of Italian nurses. Moreover, supportive therapies as hyperhydration, bladder irrigation, platelet transfusions and pain treatment are recommended by the ECIL 6 Guidelines (AIII) according to the evidence from opinions of respected authorities, thus strongly recommended for the clinical use.[29]

Nurses experiences. To date, no studies have been published regarding nurses' perceptions towards encountered difficulties while caring for patients with HC, nor on perceived outcomes. Helping patient and family caregivers to overcome the emotional burden emerged as the greatest difficulty encountered by nurses, followed by pain and symptom management and by the HC treatment itself. Frustration, dissatisfaction and anxiety emerged because of the perception of impotence. Nurses who stay close to these patients need additional support. Management of HC has been reported by our participants to increase both nurses' and other health care professionals' workloads. The impact of HC has been reported at the patient level mainly as worsening of the QoL according to previous literature.[42,43] Yasar and Akin (2016),[42] in a descriptive study including 100 Turkish patients undergoing HSCT, reported a moderate change in QoL; additionally, transplanted patients reported an inability to carry out social activities (23%) or to fulfil responsibilities (31%), and reported feeling alone (23%). Having "confidence in my nurse" has been reported as increasing the overall QoL. However, the study was not focused on patients with HC.

Our national survey is affected by several limitations, such as the low response rate that could have introduced a selection bias; moreover, we have required nurses to report their experience in terms of HC occurrence, patients, and both preventive and treatment intervention: recall bias can have affected the findings. According to the findings, no common standard of care is used in daily practice regarding HC preventive and treatment measures. Also, similar agents can be administered differently (for example, in timing and doses); moreover, any differentiation have been reported both in preventive and therapeutic measures for EOHC and LOHC. This uncertainty and the variability in daily practices reflect the limitation in preventive and especially treatment options in the field, confirmed even at the international level by the recent ECIL 6 Guidelines.[29] Therefore, to improve this clinical field, multicentre prospective clinical studies are strongly necessary: interventions based upon the best evidence could improve patients' outcomes as well as alleviate the burden on nurses who manage this clinical

condition.

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