

Outbreaks of infectious diseases in stem cell transplant units: a silent cause of death for patients and transplant programmes

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Summary:

Following the closure of the National Blood and Bone Marrow Transplant Unit in Dublin, because of an outbreak of vancomycin-resistant enterococcal infection, a survey was carried out by the EBMT to investigate the occurrence of outbreaks of infection in SCT units and the impact on patient morbidity, mortality and the administration of the transplant programme over a 10-year period from 1991 to 2001. A total of 13 centres reported 23 outbreaks of infection involving 231 patients: 10 bacterial, eight viral and five fungal outbreaks were reported and 56 deaths were attributed to infection. All fungal and bacterial deaths and the majority of viral deaths occurred in allograft recipients. In all outbreaks, the infection was reported to be hospital acquired and in all the viral, and half the bacterial infections, cross-infection was a major factor. All viral, four of 10 bacterial and three of five fungal outbreaks occurred in HEPA filtered rooms. A total of 12 SCT units reported a partial or total closure. The introduction of mandatory quality management systems such as JACIE should result in a change in attitude to 'incident reporting' and together with future surveys should reduce the incidence of infectious outbreaks in SCT units.

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Infectious complications contribute to morbidity and mortality following stem cell transplantation (SCT) and autografting. Factors that influence the risk of infection include mucosal damage caused by the conditioning therapy,¹ myelosuppression² and the presence of a right atrial catheter.³ Prior infection during remission

induction for the presenting disease⁴ or prolonged neutropenia prior to SCT may also contribute to infection in the host.⁵ The roles of graft-versus-host disease (GvHD) and its treatment in the pathogenesis of bacterial, viral and fungal infections have been well documented.⁶ Attempts have been made to reduce the impact of chemo/radiotherapy on the host by the use of reduced intensity conditioning. The pattern of infections has certainly changed but the risk of GvHD with its attendant infectious complications remains.⁷

Little attention, however, has been paid to the impact of outbreaks of infection in SCT units on patient morbidity, mortality and the administration of the transplant programme. The National Blood and Bone Marrow Transplant Unit in Dublin was closed in September 2000 following an outbreak of vancomycin-resistant enterococcal (VRE) infection.⁸ VRE was first isolated in the Haematology/Oncology Unit in January 1998. Colonisation was documented in 23 patients and infection in 10 patients during 1998 (Figure 1a). Infection control measures, including strict hand-washing protocols, isolation of patients, where possible, and attention to ward cleaning were instituted. Ceftazidime, which had been the drug of choice for febrile neutropenic episodes, was discontinued and the use of vancomycin and teicoplanin was restricted. In spite of these precautions, a further 13 patients became infected in 1999 (Figure 1b) and between June and September 2000 11 further infections were documented (Figure 1c). Factors contributing to the closure were believed to include a shortage of trained medical and nursing personnel (the number of senior nurses had fallen from 19 to 17 and junior nurses from 16 to 8.5), and a subsequent failure of measures to prevent cross-infection. Molecular typing in the Central Public Health Laboratory, Colindale, London, UK showed that the predominant strain was *Enterococcus faecalis* of the Van A type (Table 1). Health care workers were not screened for carriage of VRE.

The unit, which consisted of four six-bedded wards, each sharing one toilet, three single en suite rooms and four en suite HEPA filtered rooms, was closed for 6 months and reconstructed. During this period, all patients identified as colonised or infected with VRE were isolated in single rooms where possible, or were 'cohorted' in 'six-bedded'

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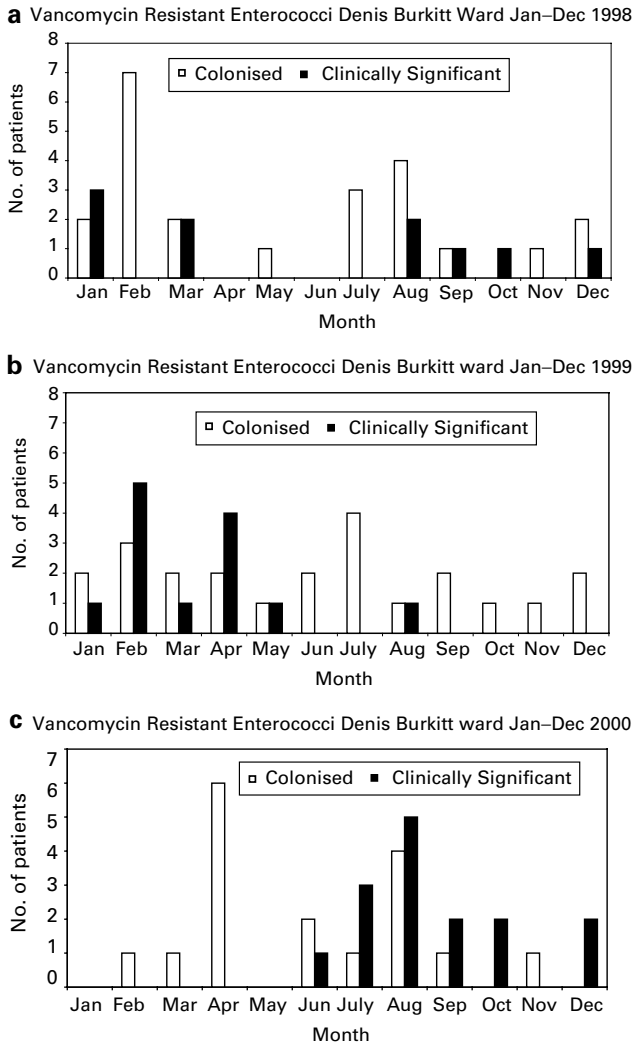


Figure 1 Incidence of colonization and clinically significant infection with vancomycin resistant enterococci from January 1998 to December 2000 in the Denis Burkitt ward at St James's Hospital.

wards where the number of beds had been reduced to four. All staff were required to wear gloves and plastic aprons when in contact with affected patients, and nursing staff were 'cohorted', where possible, to care for VRE-positive patients. A new computer function was created to identify VRE carriers on re-admission to the hospital. Mandatory education and a hard copy of the infection control policy was provided to each staff member. An information leaflet was provided for all visitors and the importance of hand washing was emphasised. In all, 15 en suite, HEPA filtered rooms were created and used exclusively for the treatment of patients with haematological malignancies and associated conditions, for example, severe aplastic anaemia. Following the Dublin experience, it became clear during conversations among EBMT members that infectious episodes had occurred in other SCT units and the Working Party decided to carry out a retrospective survey to try to elucidate the scale of the problem, its effect on the SCT programme and to highlight the importance of 'infectious outbreaks' to colleagues who might be unaware of the phenomenon.

Table 1 In all, 15 isolates of enterococci from St James's patients were compared by pulsed-field gel electrophoresis of *Sma*I chromosomal DNA digests. The banding patterns show that the *E. faecalis* isolates represent a single strain.

<i>E. faecalis</i>	PFGE profile
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	B
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	A
<i>E. faecalis</i>	C
<i>E. faecalis</i>	D
<i>E. faecalis</i>	A

Methods

Following this closure, a questionnaire was sent to 505 EBMT SCT centres in order to assess if any infectious outbreaks had occurred in the preceding 10 years (Appendix A). If a centre answered in the affirmative, a second questionnaire (Appendix B) was sent to assess the frequency of 'outbreaks' of infection, the organisms involved, the impact on patient care and the operation of the transplant programme over the last 10 years (1991–2001). An 'outbreak' was defined as an increase in the incidence of that infection, above the expected incidence in the SCT unit, with the proviso that there were no coincidental changes in the case definition of infection, mode of surveillance or the laboratory methods used to identify the infection. An infection was defined as the isolation of pathogens from a site not normally inhabited by these organisms from a patient with clinical signs or symptoms of infection. When bacteria or fungi were present in a normally sterile site or found in an area that they would not normally inhabit, in a patient without clinical signs and symptoms of infection, that individual was considered to be colonised. In all, 41 centres out of a total of 505 reporting to the EBMT returned the questionnaire.⁹

Results

A total of 13 centres reported 23 outbreaks of infection involving 231 patients between 1991 and 2001, most of them occurring in the last 5 years. Infection was the cause of death or a major contributing factor in 56 patients. In all, 10 bacterial, eight viral and five fungal outbreaks were reported. The organisms involved are shown in Table 2. Bacteria included *Pseudomonas*, *Serratia* and vancomycin-resistant *Enterococcus* (VRE); viruses were Parainfluenza and respiratory syncytial virus (RSV); and fungi included *Aspergillus*, *Scedosporium* and *Paecilomyces* sp. Molecular typing was carried out in the majority of bacterial and viral infections (Table 2). Although only five units reported outbreaks of fungal infection, the total number of deaths

Table 2 Number of outbreaks, patients infected and type of organism

Number of outbreaks	Organism	Number of outbreaks	Serotype carried out	Molecular typing carried out	Number of deaths	Unit closed	Programme stopped
<i>Bacterial 10</i>							
	<i>Pseudomonas aeruginosa</i> (three multiresistant)	4	3	3	5	One unit closed for 3 weeks and one was partially closed for 2 weeks	One programme for 2 weeks
	<i>Pseudomonas pickettii</i>	1	1	0	0	No	No
	Vancomycin-resistant enterococcus	3	0	3	0	One unit closed for 6 months	One programme stopped for 6 months ^a
	<i>Serratia marcescens</i>	1	1	1	0	No	No
	Gram negative (unspecified)	1			1	Partial closure of unit	No
Total number of patients infected = 72							
<i>Viral 8</i>							
	Parainfluenza-3	5	5	3	4	One unit closed for 1 month Three units partially closed for 2-4 weeks	Two programmes stopped for 2 weeks
	Respiratory syncytial virus	3	2	2	4		
Total number of patients infected = 106 ^b							
<i>Fungal 5</i>							
	<i>Scedosporium</i>	2			1	One unit partially closed for 6 weeks	One allograft programme stopped for 6 weeks
	<i>Aspergillus</i>	2			29	One unit closed for 2 months	No
	<i>Paecilomyces lilacinus</i>	2			2	Partial closure of one unit for 2 weeks	One programme stopped for 2 months
Total number of patients infected = 53							

^aAllograft patients were referred to a centre in the UK.

^bA total of 10 more deaths occurred in a unit with a dual outbreak of para-flu and RSV.

was 32 out of a total of 53 cases (Table 2). All the fungal and bacterial deaths occurred in allograft recipients, with a minority of viral deaths in autograft recipients (Table 3). The total number of allogeneic SCT reported to EBMT in the 10-year period was 46 915 and autografts was 88 995. In the centres reporting infectious outbreaks, the numbers were 5435 and 3846, respectively. It was unclear whether building programmes in the hospitals contributed to the fungal outbreaks. Three centres reporting fungal outbreaks mentioned building works elsewhere in the hospital or close by, but in no case were building works being carried out in the SCT unit at the time of the outbreak. All of the viral outbreaks, four of 10 bacterial and three of five fungal occurred in HEPA filtered rooms.

In all outbreaks, the responders believed that the infection was hospital acquired, and in half the bacterial and all the viral infections, they reported that cross-infection was a significant contributing factor. Cross-infection, in contrast, was not reported as a major contributing factor to fungal outbreaks. Three units

claimed that the staff were the source of transmission of viral infection and in one unit staff with symptoms of upper respiratory infection were screened.

Viral outbreaks were first reported in 1995 (Parainfluenza-3) and in 1999 (RSV), and all eight were reported from hospitals in the UK. Three of eight outbreaks were reported to occur during a community epidemic. In all, 18 patients died out of a total of 106 viral infections (Table 2).

Six patients died from bacterial infection, five from *Pseudomonas aeruginosa* (three multiresistant) and one from an unidentified Gram-negative organism.

A total of 12 SCT units reported a partial or total closure for periods of 3 weeks to 6 months (Table 2). It was difficult to obtain precise information on the effect of the closures on the transplant programme retrospectively. At least 20 patients had their transplant delayed and 13 patients were referred to other centres. Reinforcing hand-washing techniques, use of single rooms and gloving were the most popular measures taken (70%), and masks and gowns were

Table 3 Number of cases and number of deaths solely or partly due to outbreaks

	Bacterial	Viral	Fungal
<i>Number of cases</i>			
Allo-BM	34	52	49
Allo-PBSC	16	22	0
Auto	8	14	0
Others: leukaemia/lymphoma	27	5	4
<i>Number of deaths</i>			
Allo-BM	3	12	32
Allo-PBSC	3	4	0
Auto	0	2	0

used in 50% of centres. The unit in Dublin was totally rebuilt to provide 15 single en suite, HEPA filtered rooms. Since reopening in March 2001 until July 2003 a single new case of infection caused by VRE has been identified and the number of new colonised patients in 2002 was eight and in 2003 it was six (January–July).

Discussion

This survey represents only 'the tip of the ice-berg' of outbreaks in SCT units reporting to EBMT. The low number of responses to the questionnaire is most probably due to reluctance on the part of the transplant physicians to report such instances or failure to recognise infectious outbreaks in SCT units. Publication of this report will hopefully increase awareness in SCT units about the possibility of infectious outbreaks and encourage reporting of such events. Failure to provide precise information such a long time after the primary event may explain, in part, reluctance to report. The introduction of mandatory quality management systems such as JACIE in Europe (<http://EBMT.org/JACIE>) should result in a change of attitude where 'accident reporting' becomes the norm. Future surveys of outbreaks of infection by the EBMT should increase awareness of the problem. It is clear from these limited data that hospital-acquired infection is still a problem and that cross-infection remains an issue, especially in viral outbreaks.

In addition, it is important to note that the majority of deaths occurred in allograft recipients (all of the fungal deaths). The intense conditioning, the occurrence of GvHD in this population and the associated prolonged hospitalisation appear to be the major contributing factors to death. It is probable that infectious outbreaks are common in SCT units but go unrecognised.

We do not know if delays in proceeding to SCT influenced the outcome of the transplant in any patient, but the closure of SCT units and the extra work involved in investigating the outbreaks, re-education of staff and, in one case, rebuilding of the unit caused major stress on staff and patients and was costly.

Although HEPA filtration did not provide complete protection from fungal infection, there are good retrospective studies to suggest that it reduces the risk of *Aspergillus* infection, the most common airborne infection

in SCT patients.^{10–13} However, the benefits conferred by HEPA filtration require appropriate maintenance, monitoring of positive pressure and education of staff and patients.^{14–16} Previous colonisation or invasive fungal infection during periods of chemotherapy-induced neutropenia increase the risk of re-emergence of infection in the post transplant period.⁴ Contamination of water supplies may also be a source of fungal infection in the transplant recipient.¹⁷ *Pseudomonas* is water-borne and, therefore, constant monitoring of water supply is mandatory. This should be part of a surveillance programme in all SCT units.

The relationship between building works and mould infections is well-established.¹⁸ *Aspergillus* outbreaks have been reported in SCT units.^{14,19} Chazalet *et al*²⁰ have also shown that there are so many different molecular species of *Aspergillus* (approximately 800 in room air) that a correlation with types found in the patient and the air is precluded. In many instances, it is difficult to demonstrate a direct connection between hospital building and *Aspergillus* infection in transplant recipients.²¹ Many hospitals are permanent building sites, and in the outbreaks reported here most physicians did not report building works in the proximity of the SCT unit. Recommendations have been made, however, to minimise the risk of *Aspergillus* during building works in hospitals.^{22–25} Outbreaks of *Scedosporium* and *Paecilomyces lilacinus* have also been reported from SCT units^{26–28} and two are included in this survey.^{26,28} In one instance, contaminated skin ointment was the cause of the outbreak.

Viral infections have a high mortality rate in SCT units and spread is not prevented by HEPA filtration.^{29–39} A policy of influenza vaccination for all staff and the prohibition of staff working in SCT units who have symptoms of viral upper respiratory infection is appropriate. Removal of staff may, however, not be possible due to lack of availability of trained and experienced colleagues. Scrupulous hand washing and wearing of masks is advised under such circumstances.

Outbreaks of bacterial infection still cause mortality in immunocompromised hosts.^{40,41} VRE is an emerging pathogen in Europe, and the incidence of colonisation is variable.^{42–45} Provision of single rooms and attention to hand washing reduces the potential for outbreaks to occur. The Centre for Disease Control, Atlanta, has published recommendations to limit the use of vancomycin and hopefully reduce the possibility of spread of VRE in hospitals.⁴⁶ The use of vancomycin, therefore, should be strictly controlled and indications for its use should be clear. There has been no evidence of cross-infection in the Dublin unit and there has been only one new case of infection with VRE since the reopening of the unit in February 2001. All patients are treated in single en suite rooms, and adequate nurse/patient ratios have been maintained. A continuing education programme for all staff working in the unit is carried out by infection control staff members, and random checks on hand-washing techniques are carried out (S McCann, personal communication).

While significant progress has been made in the prevention and management of many infections due to reactivated

pathogens (ie, cytomegalovirus), little has been done to reduce the risk of infection contracted from staff, the hospital environment or the community by transplant patients. This study shows that outbreaks are an additional cause of death in SCT recipients. Many of the outbreaks reported here could probably have been controlled or avoided by relatively simple measures. Rapid isolation of infected staff members or patients may have contained viral outbreaks. Likewise, adequate isolation of patients with VRE may have reduced the risk of cross-infection. Nosocomial aspergillus infection can be reduced with good management of air filters.

A specific, comprehensive approach to all infections in SCT units, including hospital infections, with quality indicators should be implemented as proposed in the JACIE programme. To date, we still do not know the most effective preventive measures to use, for example, laminar air flow (LAF), HEPA filtration, reverse isolation and the wearing of masks and gowns. The introduction of new therapeutic modalities such as reduced intensity conditioning stem cell transplants and out-patient transplants will make it more important that there is rapid diagnosis of outbreaks and rapid exchange of information within transplant units and between centres. This requires a close collaboration between the transplant physicians and nurses and the infection control staff. Attention to hand-washing techniques and the possibility of water-borne infections should be emphasised. The occurrence of viral respiratory tract community outbreaks should alert the team to the possibility of infection in the SCT unit. A rapid response to community outbreaks by instituting appropriate measures is required.

As the care of patients with haematological malignancies becomes more complex, awareness of the possibilities of nosocomial infection and infectious outbreaks in SCT units becomes paramount. Reporting of such events in a standardised manner, collection and analysis of data and conducting prospective studies to assess the efficacy of measures taken will be a challenge to transplant teams and organisations such as the EBMT. It is hoped that the publication of this report will increase the level of awareness and willingness to 'report' outbreaks of infectious diseases in SCT units.

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Appendix A

EPIDEMICS IN SCT UNITS

A SURVEY of the EBMT INFECTIOUS DISEASES WORKING PARTY

Shaun Mc Cann, Alois Gratwohl, Catherine Cordonnier

Background: SCT teams have occasionally reported epidemics due to bacterial, fungal, or viral agents, occurring in their wards. These epidemics seem to be rare but may be responsible for morbidity and mortality in the transplant population, raise major problems for controlling infection, and have practical impact on the transplant program. Moreover, they may have economical and legal consequences. In order to prevent epidemics, and to help EBMT centers to rapidly recognize and control epidemics in the transplant wards, the IDWP run this survey. We thank each of you in advance for your participation.

Objective: The objective of this survey is to identify the main origins and pathogens responsible for epidemics in European SCT units over the last 10 years, in order to elaborate recommendations for the prevention and policies for epidemics in the EBMT centers.

The objective of the survey is not to identify individual risk factors for infection during epidemics, but only to look at:

- the main pathogens involved
- the mortality related to the epidemics in the transplant population
- the practical impact of the epidemics on the transplant program
- the methods implemented for controlling infection

Definitions (from *Epidemics: Identification and management*. B.N. Doebbeling, in *Prevention and Control of Nosocomial Infections*, 2nd Edition, Wenzel RP Ed.)

An epidemic or outbreak of nosocomial infections is defined as a statistically significant ($p < 0.05$) increase in the incidence of a specific infection above that noted previously in a certain patient population, as far as no change occurred during that time in the case definition, surveillance, or the laboratory techniques to identify the infecting agent

Methods

- 1) A first questionnaire (enclosed) will collect global retrospective data on epidemics in the EBMT centers between 1991-2001.
- 2) For centers who will accept, a short additional questionnaire will be sent to collect the attack rate before, during, and after the epidemics, and the attributable mortality in the SCT population.

EBMT CIC:	Hospital:
Reporter:	Date of report:
Fax:	@mail:

1) Your center participate in a surveillance program for nosocomial infections in your hospital?
 Yes No

2) From when are you able to report on epidemics in your unit:

3) **Between 1991-2001, your center experienced any epidemics as defined below**

No. If No: Please return only the first page of the questionnaire to:

Catherine Cordonnier Fax 33 1 49 81 20 67

Yes. If Yes: Please fill page 2 before returning the questionnaire

EPIDEMICS IN SCT UNITS (1991-2001)

Questionnaire 1, page 2 (EBMT IDWP June 2001)

If you experienced any epidemics, please fill this questionnaire:

1 - Year of the epidemics. If more than one, please give date of each epidemic:

2 - Duration of the epidemics (1st case to last case, in months).....

3 - Pathogen involved (please circle):

- BACTERIA: MRSA, VRE, Salmonella, C. difficile, Gram negative bacteria, mycobacteria, legionella, other (specify)

- FUNGI: Aspergillus, Candida, other: specify

- VIRUS: Adenovirus, RSV, Influenza, Para-influenza, Rotavirus, Polio, other: specify

- Pathogen unknown: please comment

4 - Were the epidemics microbiologically confirmed (molecular typing, serotyping) ?

Yes

No

5 - Was the cause (i.e., hospital renovation for aspergillus) of the epidemics identified ?

Yes

No

6 - Which kind of units was involved?

"Sterile unit": HEPA filters

Yes No

LAF rooms

Yes No

Open ward

Yes No

Daycare center

Yes No

7 - How many cases of infection were observed during the epidemics?

Autologous SCT patients:..... Allogeneic recipients: PBSC..... BM.....

8 - How many transplant patients died from the infection during the epidemics?

Autologous SCT patients:..... Allogeneic recipients: PBSC..... BM.....

9 - Did you: close a part of the transplant ward?

close all the transplant ward?

stop the transplant program?

If yes, for how long :

Comments:.....

.....

.....

10 - Do you agree to receive the second questionnaire (1 page) for this survey ?

Yes

No

Thank you to send the 2 pages of this form, back to:

Catherine Cordonnier

Service d'Hématologie

Hopital Henri Mondor, 94000 Créteil, France

Fax: 33 1 49 81 20 67 carlcard@worldnet.fr

6 - Whatever the pathogen involved:

- Were other cases observed in other departments (organ transplant departments, intensive care etc..)
in your hospital? Yes No

If yes, please specify:.....

- Was the outbreak considered as hospital acquired? Yes No

- If yes, were the cases

due to a common environmental source

due to a therapeutic device:aerosol , IV solution Please specify:.....

due to cross infection

unknown

7 – Methods implemented for controlling infection?

Identifying the source in the environment: Yes No

Air samples Surface samples Water samples

Other. Please specify (i.e., devices, IV solutions)

.....

Screening the staff for the pathogen Yes No

Screening all the patients for the pathogen Yes No

Closing a part of the transplant ward Yes No

Closing all the transplant ward Yes No

Modifying the transplant programme Yes No

Stopping the transplant programme Yes No

If the transplant program was stopped: date of stopping the programme:/...../.....

date of starting the programme again:/...../.....

Prophylactic measures:

Prophylactic drugs Yes No

(please specify).....

Cohorting (regrouping colonized or infected patients in a specific area) Yes No

Re-inforcing isolation procedures (more than one is possible):

Private room Yes No

Gloving Yes No

Re-inforced hand-washing Yes No

Masks Yes No

Gowns Yes No

Other (Specify).....;

Identification of infected or colonized patients (doors, charts ...) Yes No

Specific educational program for staff

O Yes O No

8 – If you stopped or delayed the transplant program, did some patients suffer from that measure:

- Number of patients whose transplant was delayed:
- Number of patients who relapsed or died or worsened due to the delay:
- Number of patients referred for transplant to another centre:

9 Do you have any comments?

EBMT CIC	Hospital:
Reporter:	Date of report:
Fax:	@mail:

Thank you to send this form on March 10 at the latest to:

**Shaun McCann
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