



RAPID RISK ASSESSMENT

Potential contamination of Viaspan® organ perfusion solution

23 April 2012

Main conclusions and recommendations

An organ perfusion solution known as Viaspan® has been identified as being potentially contaminated with *Bacillus cereus*. Viaspan®, which is used to preserve organs prior to transplantation, is distributed to a number of countries around the world. Solid organ transplant recipients are a vulnerable population who, due to profound immunosuppression, are more susceptible to infections and their sequelae. *Bacillus cereus*, a ubiquitous organism, has been reported as a pathogen in immunosuppressed patients, especially in association with contaminated medical products or devices.

The likelihood of contamination and risk of infection in recipients or potential recipients of organ transplants preserved in Viaspan® solution produced after July 2011 appears to be low, based on the negative results of microbiological cultures in solution samples and the absence of reported patient cases to date. Nevertheless, vigilance is recommended.

To mitigate the risk, the following approach should be considered:

- Patients who have undergone transplantation with organs or tissues kept in Viaspan® since July 2011 should be monitored for early detection of symptoms and signs of infection. Clinicians and laboratories should be alerted to the potential risk.
- In the event that a patient who has received an organ previously exposed to this solution presents with symptoms and signs of infection, a thorough microbiological investigation should be conducted. *B. cereus* should be considered a cause rather than a contaminant if isolated from clinical specimens.
- All decisions regarding antibiotic therapy should be the responsibility of the treating physicians, taking into account available susceptibility results and patient-specific factors. All *B. cereus* isolates detected by culture should be tested for antimicrobial susceptibility in order to appropriately tailor the antibiotic therapy to the patient's needs. Empiric antibiotic therapy, pending results of the microbiological investigation, should include antibiotics which have been reported susceptible by the manufacturer, Bristol-Myers Squibb, and the UK Health Protection Agency (HPA).
- For patients who need to undergo transplantation of organs or tissues preserved in the Viaspan® batches produced since July 2011, treating physicians should consider adapting antibiotics used for peri-operative antibiotic prophylaxis to include those to which *B. cereus* is likely to be susceptible, taking into consideration the list of antibiotics active on *B. cereus* provided by both Bristol-Myers Squibb and UK HPA.
- Alternative preservation fluids for organs and tissues should be considered whenever possible.

Source and date of request

Request from the Directorate General for Health and Consumers, Unit D4 – Substances of human origin on 3 April 2012 at 16:32.

Questions:

- How dangerous is the solution for transplanted patients?
- Is there any risk of transmission from transplanted patients to other persons?
- Is there a treatment which could be recommended?

Public health issue

A risk to patients having undergone or likely to undergo transplantation with an organ potentially contaminated with *Bacillus cereus*.

Consulted experts

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Disease background information

Bacillus cereus is a spore-forming Gram-positive aerobic or optionally anaerobic bacterium that is widely distributed in the environment and can be found in soil, dust, decaying vegetal matter, insects and various food items. The organism is capable of producing a variety of exotoxins such as emesis-inducing toxin, causing vomiting and diarrhoea if ingested, as well as cytotoxins causing haemolysis and tissue necrosis if released at the site of infection following traumatic or parenteral inoculation (1). In addition to food poisoning through ingestion of the pre-formed toxin, *B. cereus* has been reported as a cause of potentially lethal extra-intestinal infections, including post-traumatic skin wound infections, gangrene, endophthalmitis, necrotising pneumonia, bacteraemia, endocarditis, meningitis, brain and intra-abdominal abscesses. These invasive infections have mostly been reported among immunocompromised patients such as those with acute leukaemia, as well as in intravenous drug abusers, and neonates (2). Between 1979 and 2010, fifteen nosocomial outbreaks caused by *B. cereus* were reported in literature. In six outbreaks the source of patient contamination was traced to a contaminated medical device, in four to a food item, in a further four to fomites and in one to a contaminated medical product (ethyl-alcohol antiseptic solution).*

Bacillus cereus produces a potent beta-lactamase that mediates resistance to beta-lactam antibiotics, including all cephalosporins. Therefore, standard peri-operative surgical prophylaxis may not be effective in preventing post-surgical infection if *B. cereus* is contaminating the surgical site. *Bacillus cereus* is generally susceptible to vancomycin, ciprofloxacin, linezolid, daptomycin, clindamycin and carbapenems but resistance may occur and therefore antibiotic susceptibility testing of invasive clinical isolates is recommended (3).

Solid organs harvested from donors prior to transplantation are usually kept in hypothermic conditions and are transplanted within a few hours (4). Solid organs are often washed with antibiotic solutions prior to transplantation (5). Both the low temperature and antibiotic washing do not favour the growth of bacteria but potential elimination of *B. cereus* depends on the antibiotics chosen for this process. Because this organism is spore-forming, it can resist exposure to disinfectant and topical antibiotics in spore form until it germinates to vegetative cells, a phenomenon that may take place only after entering host tissue (2).

Infections after transplantation depend largely on the exposure of the patient, and immunosuppressive status. The degree and choice of immunosuppression administered to a patient after transplantation is dependent on a variety of factors, including the parameters of the host, the type of organ transplanted and the results of screening for active or latent infections in the donor of the organ. Infections in the immediate post-operative period (Days 1–30) following transplantation are mostly associated with either bacterial infections due to complications in surgical technique, healthcare-associated infections (e.g. surgical site, ventilator-associated) or the transmission of donor-derived infections (6).

* Source: www.outbreak-database.org

Event background information

On 19 March 2012, Bristol-Myers Squibb was informed by Fresenius Kabi Austria of a failure in a routine media fill procedure on the production line of Viaspan®, a preservation fluid for maintaining organs and tissues from time of procurement to transplantation. *Bacillus cereus* had been found during the media fill process (a manufacturing process to check sterility), but not in Viaspan® bags.

On 21 March, Bristol-Myers Squibb notified the event to the relevant health authorities in the United Kingdom. One day later, Bristol-Myers Squibb UK informed the UK Medicines and Healthcare products Regulatory Agency (MHRA) of the potential product contamination. A national competent authority report (NCAR) was produced.

On 29 March, the Austrian Federal Office for Safety in Health Care issued a rapid alert notification of a quality defect/recall, listing the action taken as 'monitoring of the investigations at the manufacturer and reviewing if an alternative product is available'. The proposed action was the recall of affected batches if alternative products were available. According to this notification, the product had been distributed to Argentina, Australia, Austria, Belgium, Brazil, Chile, Croatia, Denmark, Estonia, Finland, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Lithuania, the Netherlands, New Zealand, Norway, Poland, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom. Bristol-Myers Squibb stated that the product is not marketed in the US. In the proposed action it was also noted that, if no alternative product was available, Bristol-Myers Squibb would contact the appropriate national competent authority to discuss maintenance and whether the product was marketed as a medicinal product or a medical device (7).

The same day, Bristol-Myers Squibb communicated safety information and guidance to healthcare professionals (8) and a field safety notice to pharmacists, wholesalers, transplant centre directors and co-ordinators (9), informing them of the precautionary recall of all batches manufactured since 8–9 July 2011. This information included advice on action to be taken by the user.

A letter was issued by MHRA to clinicians (10) with an update on the situation, suggesting advice on the use of alternative products, increasing awareness and appropriate control measures. The letter also stated that the UK blood and transplant agency (NHS Blood and Transplant) and MHRA had not been made aware of any adverse reactions since July 2011, the possible date since when batches could potentially have been contaminated.

The product was recalled as a precautionary measure on 30 March 2012 (7).

The Fresenius Kabi company in Austria has been producing the organ perfusion solution (Viaspan®) since 2006. The responsible microbiologist at Fresenius Kabi reported that the company conducts a 'media fill' twice a year. This is a simulation of the production process which involves filling lines using a nutrition solution for bacterial growth as medium to reconfirm aseptic processing. The last media fill test, conducted in February 2012, revealed that of 2 950 bags, 369 (13%) were contaminated with *B. cereus* and *B. thuringiensis*. Previously performed media fill tests were negative for bacterial growth.

According to the information from Bristol-Myers Squibb, on 30 March, they have carried out a precautionary product recall to the retail/dispensing level of all lots of Viaspan® 50mg/ml manufactured by Fresenius Kabi since July 2011. The recalls were promptly implemented in the countries where alternatives are readily available (Argentina, Chile, Estonia, France, Germany, Ireland, Italy, Slovenia, Switzerland and the United Kingdom). In countries where no immediate alternative solution is available, Bristol-Myers Squibb will be working with the local health authorities to find alternative solutions for patients before issuing the recall (Australia, Belgium Croatia, Denmark Finland, Latvia, Lithuania, the Netherlands, New Zealand, Norway, Spain and Sweden) (7).

Following the media fill failure in February 2012, the search for a source of contamination identified a defective valve associated with a defective pressure gauge as the most probable cause for the environmental microorganisms entering into the production line. According to Fresenius Kabi, it was most likely that the problem started when the gauge was reinstalled in August 2011 (11).

Additional product testing performed by Fresenius Kabi from 12 April showed that four Viaspan® batches currently on site and retained samples of Viaspan® batches 'on hold/recalled' have all passed the sterility test. A study of the growth behaviour of *B. cereus* revealed that under 4°C storage conditions, the *B. cereus* strain was not capable of growth in Viaspan®. The Viaspan® market storage conditions are between 2°C and 8°C.

Antibiotic susceptibility testing of the *B. cereus* strain isolated in the media fill process showed that it is sensitive to clindamycin, erythromycin, moxifloxacin, gentamicin, imipenem, linezolid, tigecycline and vancomycin, and resistant to cefepime, cefuroxime, penicillin and ampicillin (11).

Concomitant tests performed by the UK HPA National Reference Laboratory on antimicrobial susceptibility for the isolates of *B. cereus* from the contaminated lines have shown susceptibility to linezolid, tigecycline, doxycycline, tetracycline, ciprofloxacin, moxifloxacin, erythromycin, chloramphenicol, gentamicin, streptomycin and resistance to penicillin, amoxicillin-clavulanate, cefotaxime, vancomycin, daptomycin, rifampicin and clindamycin (12).

Furthermore, results of growth behaviour testing showed that *B. cereus* was unable to grow at temperatures below 4°C but was able to grow at room temperature. The recommended storage temperature of Viaspan® is 2–8°C (11).

ECDC threat assessment for the EU

Is there a risk for patients who have received organs potentially contaminated?

The risk to patients of developing an infection with *B. cereus* depends on the likelihood of the Viaspan® perfusion solution being contaminated and other factors listed below:

- The microbiological characteristics of the implicated *B. cereus* strain;
- The inoculum of *B. cereus* contaminating Viaspan®;
- The immune status and co-morbidities of the transplant recipients;
- The type of solid organ being transplanted and the type of immunosuppressive regimen administered.

Clinical presentation of infection in transplant recipients may vary and can be altered or muted because of their level of immunosuppression or the antibiotics that they have received, leading to diagnostic delay of infection (13).

To date, no cases of infections with *B. cereus* have been reported from transplant recipients who have received solid organs preserved in Viaspan® solution. Additionally, samples from four Viaspan® batches on stock at the manufacturer Fresenius Kabi Austria and samples from another four batches taken from 'on hold/recalled' market batches have all passed sterility testing (14). Based on these data, the likelihood that Viaspan® has been contaminated appears to be low, but it cannot be completely excluded unless every single unit of Viaspan® is tested individually (11).

Since culture results from the tested Viaspan® batches have not indicated contamination with *B. cereus* and no infections have been reported from transplant recipients so far, the risk of infection appears to be low. We cannot, however, state with certainty that *B. cereus* is not able to grow in Viaspan® solution kept above 4°C, since the growth behaviour tests were indicative for storage conditions below 4°C. In addition, even a low inoculum contamination of transplanted organs may be sufficient to initiate post-operative infection.

Is there a risk for patients who will undergo transplantation in future?

For countries opting to continue to use Viaspan® due to the lack of alternative solutions, the risk of infection with *B. cereus* from contaminated Viaspan® solutions for future recipients is low, and probably similar to that for patients who have received organ transplants preserved in the solution since July 2011.

Is there any risk of transmission from transplanted patients to other persons?

Although *B. cereus* is ubiquitous in the environment, there are no documented cases to date reporting transmission of *B. cereus* from infected transplant recipients to other individuals. It is recommended, however, that standard precautions be used in healthcare facilities if patients are known to be infected with this organism (15).

Is there a treatment which could be recommended?

For treatment purposes antibiotic susceptibility data should be based on the resistance patterns of *B. cereus* available from reports published in literature and those made available by Bristol-Myers Squibb. The national reference laboratory for antimicrobial resistance at HPA (UK) has also performed susceptibility testing, using more than one quantitative method, on a number of isolates detected from the media fill and has made its findings available.

Results from testing by Bristol-Myers Squibb showed that the *B. cereus* isolates were susceptible to all antibiotics tested, with the exclusion of beta-lactams (penicillins and cephalosporins) to which *B. cereus* is known to be resistant (3). Furthermore, testing by HPA (UK) indicated that there was intermediate resistance to vancomycin in several isolates and resistance to clindamycin in one isolate. Additional resistance to daptomycin, rifampicin and clindamycin was also reported. These observed differences between Bristol-Myers Squibb and the HPA (UK) laboratory results in susceptibility may be explained by differences in the methods used, but it is also important to highlight that there are no national or international recommended breakpoints for clinically categorising the antibiotic susceptibility of *B. cereus*.

When antibiotics are selected for peri-operative prophylaxis or when therapy is being considered for confirmed or suspected infection with *B. cereus* in potentially exposed patients, they should include agents that are selected from the remaining antibiotics to which these isolates are reported susceptible.

Antibiotic selection for therapy, however, should always be adapted to the patient's clinical condition and final results of susceptibility testing on clinical isolates recovered from the individual patient.

Conclusions

Solid organ transplant recipients are a vulnerable population who, due to their profound immunosuppression, are more susceptible to infections and their sequelae. *Bacillus cereus*, a ubiquitous organism, has been reported as a pathogen in immunosuppressed patients in the literature, especially in association with contaminated medical products or devices.

Although, based on the negative results of microbiological cultures from the manufacturer and no reported patient cases to date, the likelihood of contamination and the risk of infection in recipients or potential recipients of organ transplants preserved in Viaspan® solution produced after July 2011 appears to be low. Nevertheless, vigilance is recommended.

To mitigate the risk of surgical infection caused by *B. cereus* in Viaspan® solution to solid organ transplant recipients, the following approach should be considered:

- Patients who have undergone transplantation with organs or tissues kept in Viaspan® since July 2011 should be monitored for early detection of signs and symptoms of infection are detected. Clinicians and laboratories should be alerted about this potential risk.
- In the event that a patient who has received an organ previously exposed to this solution presents with symptoms and signs of infection, a thorough microbiological investigation should be conducted and *B. cereus* considered a cause rather than a contaminant if isolated from clinical specimens.
- All decisions regarding antibiotic therapy should be the responsibility of the treating physicians, taking into account available susceptibility results and patient-specific factors. All *B. cereus* isolates detected by culture should be tested for antimicrobial susceptibility in order to appropriately tailor the final antibiotic therapy to the patient's needs. Empiric antibiotic therapy, pending results of the microbiological investigation, should include antibiotics which have been reported susceptible by Bristol-Myers Squibb and HPA (UK).
- For patients who need to undergo transplantation of organs or tissues preserved in the Viaspan® batches produced since July 2011, treating physicians should consider adapting antibiotics used for peri-operative antibiotic prophylaxis to include those to which *B. cereus* is likely to be susceptible, taking into consideration the list of antibiotics active on *B. cereus* as provided by both Bristol-Myers Squibb and the HPA (UK).
- Alternative preservation fluids for organs and tissues should be considered whenever possible (10).
- There is no documented evidence of person-to-person transmission of this organism. The risk of transmission of *B. cereus* from transplant patient recipients to other individuals appears to be very low and does not warrant more than standard precautions.

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