'Sterility Testing of Blood Components and Advanced Therapy Medicinal Products' (Munich, April 29, 2010) Organized by the DGTI Section 'Safety in Hemotherapy' – Meeting Report

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Keywords

Sterility testing · Bacterial contamination ·
Blood components ·
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Summary

Neither screening method completely detects all clinically relevant bacterial contaminations. The effect of sampling time and volume as well as standardization of the assay applied has also to be taken into account. Therefore, minimizing the risk of contamination during manufacture by measures such as donor selection, skin disinfection, division, and processing within closed systems remains crucial. In this context new concepts in sterility testing, especially with instable advanced therapy medicinal products (ATMPs), are needed as well as reassessment of pathogen inactivation techniques. At present hemovigilance data indicate that shortening the shelf life of platelet concentrates as introduced in Germany 2008 reduced the risk of transfusion-transmitted bacterial infections to the same extent as bacterial screening as done in Canada or the Netherlands. The evolving methodological progress, e.g. by standardizing culture methods or enhancing detection systems, requires careful follow-up in parallel to hemovigilance data in order to ensure optimal bacterial safety in hemotherapy.

Schlüsselwörter

Sterilitätsprüfung · Bakterielle Kontamination ·
Blutkomponenten ·
Arzneimittel für neuartige Therapien · Hämovigilanz

Zusammenfassung

Kein Suchtest erfasst alle klinisch relevanten bakteriellen Kontaminationen vollständig. Auch muss der Einfluss des Zeitpunkts und des Volumens der Probenahme sowie der Standardisierung des verwendeten Testverfahrens bedacht werden. Daher bleibt die Minimierung des Kontaminationsrisikos bei der Herstellung durch Maßnahmen wie Spenderauswahl, Hautdesinfektion, «Predonation-Sampling» und Verarbeitung im geschlossenen System entscheidend. In diesem Zusammenhang bedarf es sowohl neuer Konzepte bei der Sterilitätsprüfung, insbesondere bei instabilen Arzneimitteln für neuartige Therapien (ATMPs), als auch einer Neubewertung der Methoden zur Pathogeninaktivierung. Aktuell belegen Hämovigilanzdaten, dass die Verkürzung der Haltbarkeit von Thrombozytenkonzentraten, wie sie 2008 in Deutschland eingeführt wurde, das Risiko von transfusionsbedingten bakteriellen Infektionen im gleichen Umfang reduziert wie die systematische Untersuchung auf Bakterien, wie sie in Kanada oder den Niederlanden durchgeführt wird. Die kontinuierlich fortschreitende methodische Entwicklung, z.B. durch Standardisierung der Kulturmethode oder Verbesserung der Detektionssysteme, muss parallel zu den Hämovigilanzdaten sorgfältig weiter verfolgt werden, um die optimale mikrobiologische Sicherheit in der Hämotherapie zu gewährleisten.

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Introduction

The implementation of more sophisticated screening methods for infectious diseases including nucleic acid testing (NAT) has significantly reduced the risk of transfusion-transmitted virus infections [1]. Thus, bacterial contamination of blood components and ATMPs – the cause of transfusion-related septicemia – has become a major concern in optimization of hemotherapy safety [2]. In Germany, the National Advisory Committee ‘Blood’ (Arbeitskreis Blut) of the German Federal Ministry of Health recommended to reduce the shelf life of platelet concentrates (PCs) to 4 days (Votum 38, June 9, 2008) [3]. Other countries have introduced bacterial screening to reduce the risk of transfusion-related septicemia. At the same time, design and development of methods for the detection of relevant bacteria in blood products has been in progress. The meeting was held in Munich on April 29, 2010 to give an overview of the current state-of-the-art on an international level. The speakers’ abstracts are also presented in order to provide the interested reader with all results in detail. The following report is meant to be suggestive of this exciting topic.

Strategies in the Netherlands, the UK, and Canada

Dr. Dirk de Korte, Sanquin Blood Supply Foundation, Amsterdam, The Netherlands, reported on mandatory bacterial screening of blood components applying culture methods from 2001 and the 50% reduction of bacterial contamination of PCs after implementation of diversion (‘predonation sampling’) in 2004. Before that, changing the skin disinfection method resulted in a 10% reduction of bacterial contamination.

This was in contrast to the results of Dr. Carl P. McDonald, National Health Service Blood Transplantation, London, UK, who found a greater decrease in bacterial contamination by this measure (57%) and a similar effect by diversion (66%). From hemovigilance data the effect of these measures were considered inadequate so that mandatory bacterial screening of PCs will shortly be implemented.

Dr. Sandra Ramirez-Arcos, Canadian Blood Services, Ottawa, ON, Canada, calculated from her bacterial screening data covering more than 5 years a chance of 1 of 2,621 and 1 of 4,768 true or suspected positive culture results in apheresis platelet concentrates (APC) and buffy-coat platelet pools (BCPC), respectively. Unconfirmed initially positive cultures due to machine failures accounted for the majority of false-positive results.

Transfusion-Related Bacterial Infection: The Effect of Bacterial Screening

These extensive efforts could not prevent transfusion-transmitted bacterial infection (TTBI): From the presentations

of de Korte, McDonald, Ramirez-Arcos and a report of the Paul Ehrlich Institute [4] transmissions per 10^6 PCs transfused were calculated to amount to ~4.5 in the Netherlands and Canada with mandatory bacterial screening as compared to ~10 in the UK and Germany without. In Germany, the reduction of the shelf life of PCs to 4 days (4×24 h) in 2008 resulted in a decrease of TTBI to 4.5 per 10^6 PCs transfused in 2009 [4]. In the UK, the implementation of mandatory bacterial screening of PCs is under way as stated by Dr. McDonald.

Detecting Bacterial Contamination: Methods, Standards, Concepts

Dr. Michael Schmidt, German Red Cross Blood Service, Institute Frankfurt, Germany, outlined the problem of these false-negative results in bacterial culture methods. Due to growth-supporting conditions during storage of PCs an initially drawn sample may yield a negative result in a culture system despite excellent sensitivity (detection limit <1 CFU/ml). Recent bacterial detection methods as well as upcoming assays and those under development e.g., FACS or NAT are more rapid test systems than culture methods. They were considered superior despite lower analytical sensitivity because they could be applied shortly before distribution of PCs.

Due to the lack of standards with relevant bacterial species and strains for the evaluation of blood components, Dr. Melanie Störmer, Paul Ehrlich Institute, Langen, Germany, had performed an international multicenter study on a newly developed panel of deep-frozen Transfusion-Relevant Bacteria Reference Strains (TRBRS). Identity, counts, and growth of bacteria in the samples were consistently reproduced by all participating laboratories. The panel will be extended to other species in the near future.

Dr Christian Gabriel, Red Cross Transfusion Service of Upper Austria, Linz, Austria, demonstrated best practice in development of an in-house real-time PCR protocol for the detection of bacterial 16s rDNA. Contaminated reagents turned out to be crucial so that a screening for contamination was introduced. Although no direct comparison in sensitivity with the culture system can be performed, the method has proved to be feasible and safe for routine application before issuing APCs.

Dr. Thomas Montag, Paul Ehrlich Institute, Langen, Germany, proposed a new concept concerning sterility testing in ATMPs or cell products applied in novel therapeutic strategies. Due to their in some cases extremely short shelf life, sterility testing requires robust and rapid methods with a reasonable sensitivity. Hence, the testing as such should be considered only as part of a complex strategy in aseptic manufacture, yielding a product for clinical application which is most likely but not certainly sterile.

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