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Transfusion-Associated Bacterial Sepsis

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1. Introduction

Transfusion-associated bacterial sepsis (TABS) is caused by bacteria present in blood components. It is one of the earliest recognized adverse transfusion-associated reactions. Blood components most often become contaminated while blood is being collected from a donor; more seldom in the case of asymptomatic bacteremia or erroneous blood processing procedures (1). Although the risk for transfusion-associated bacterial sepsis has diminished considerably since the introduction of new methods of bacteria detection and of increasingly better means of skin disinfection, reappearing reports about severe or fatal reactions after contaminated blood component transfusions prove that the problem is still very serious. Most often bacterial contamination affects red blood cell concentrates and platelet concentrates. There have been cases reported of bacterially contaminated plasma or cryoprecipitate, although bacteria do not proliferate in these components when they are stored (1,2). Of note, bacterial sepsis is an adverse reaction not only after allogenic transfusions but also after autologous ones.

Bacteria are very rarely transmitted during blood component transfusion, but if they are, they usually cause severe, life-threatening adverse reactions, with the mortality rate of 20 – 30%. In USA, bacteria transmission during transfusion is the second (just after "administrative error") most common cause of fatal transfusion-associated reactions. It is estimated that every year 100 – 150 patients undergoing blood component transfusion die because of that (1). This number is probably underestimated. There are a few causes of this situation. Tests which can confirm or exclude the infectious background of adverse reactions occurring during or right after transfusion are not always performed. Besides, the organism's response to infection may be misinterpreted as a manifestation of the underlying disease or another non-infectious transfusion-associated reaction. That is why the estimated prevalence of fatal adverse reactions may be overestimated because the adverse reactions that have the most severe course are predominantly reported to the relevant registering centers.

The risk for transfusion-associated bacterial sepsis results from the nature of pathogens themselves and from determinants connected with blood donors and recipients.

From the transfusiology point of view, the characteristic features of infectious agents include their biology, the course of infection, the degree of infectivity, and how harmful they are for the recipient if transfusion-associated bacterial infection occurs. The crucial issues are whether:

- An infectious agent is present in blood in the course of infection, how long it has been there, at what concentration;

- An infectious agent is transmitted via transfusion. Can its transfusion infectiveness be limited and how?

- In a particular population, an infectious agent is highly prevalent or not. Consequently, how many recipients are infected with it via other ways than blood component transfusions? How prevalent this infection is among donors and whether identifying uninfected donors is possible and feasible.

- An infectious agent causes a severe disease if it is transmitted with blood. Is the disease potentially lethal? What are the possibilities of treating the recipient who has acquired the disease?

The infectious agents important from the transfusiology point of view are those which are asymptomatic enough so that a donor would not report them before donation.

Infectious agents can be present only in some blood components. There are bacteria that are observed in the free form in plasma. An important parameter is also how infectious agents behave in the conditions at which blood is stored. These conditions differ for various blood components. The whole blood, its cellular components, plasma or plasma-derived preparations are stored in different forms, e.g. liquid or frozen at -25ºC to +24ºC. Most bacteria are able to proliferate in the components stored. There are also such that are very sensitive and quickly die once they are outside the host's organism. They include *Treponema pallidum*, which cannot survive longer than 72 hours at +4ºC. The fact that bacteria have been transmitted with blood does not necessarily mean that the recipient will fall ill. To a large extent, it depends on the amount of the infectious agent, i.e. how much of the blood component has been transfused and how big concentration of the pathogen was in the component. Whether a recipient will fall ill depends on the recipient's immune condition and the possibility to control the infection (3,4,). Table 1 itemizes what promotes transfusion-associated bacterial sepsis development.

• Volume of blood component transfused
• Bacteria concentration in blood component
• Immune and general conditions of recipient
• Extent of surgery, type of invasive diagnostic procedures
• Intensity of recipient monitoring
• Mode of treatment (antibiotics)

Table 1. Parameters promoting sepsis development following transfusion of bacteria contaminated blood components (5).

2. Causes of transfusion-associated bacterial sepsis

The sources of bacterial infections may be endogenous or exogenous. Bacteremia in a donor may be an endogenous source of blood sample contamination. Chronic bacteremia is observed in syphilis. Being a carrier of *Borrelia burgdorferi*, responsible for borreliosis, a tick-derived disease, or *Brucella abortus*, may also be associated with risk. Bacteremia accompanying alimentary tract infections and alimentary toxicosis in donors is caused by such bacteria as *Salmonella* but is very rare. In order to exclude them, it is important to take a comprehensive history of the donor.

Another cause of bacterial contamination of the blood collected may be by bacteria present on the donor's skin when a needle is inserted into a vein or contamination during blood collection or processing of blood components.

The risk an infection is transmitted with a blood component depends mainly on the conditions and time a component has been stored before it is transfused to a patient. It is much higher when platelet concentrates are used than in the case of red blood cell concentrates, mainly due to the storage temperature. The risk exists when it is stored in a temperature which is suitable for bacterial survival and proliferation. Platelets are the component that is stored in the conditions which promote bacterial proliferation (room temperature). Red blood cells, stored at +4ºC, are much less dangerous, and in the case of plasma or cryoprecipitate transfusion, the risk for bacterial complications is almost nil. Plasma is frozen, after it is processed at -30ºC or lower, which practically eliminates the possibility for bacteria to survive. Table 2 presents possible causes of blood component bacterial contamination.

• Asymptomatic bacteremia in donor
• Inadequate disinfection of venopuncture site
• Donor's skin fragment placed in blood container (via needle)
• Contaminated blood sampling kit or anticoagulant

- Faulty sterilization
- Wrong storing

Table 2. Causes of bacterial contamination of blood components

Bacterial proliferation in a blood sample is limited considerably by antibacterial features of blood itself. Bacteria are destroyed by the complement and phagocytized by blood leukocytes. The risk of donor-derived infection is lower after the leukocytes which have phagocytized bacteria in blood have been removed.

The severity of adverse transfusion-associated bacterial reactions which may occur in a recipient after a contaminated blood component has been transfused depends on many factors, which are presented in Table 3.

• Number of bacteria (dose)
• Types of bacteria (Gram-positive, Gram-negative)
• Virulence of bacteria – production of exotoxins and endotoxins
• Recipient's general condition (immune system functioning, underlying disease)
• Recipient undergoing antibiotic therapy

Table 3. Factors influencing the severity of transfusion-associated adverse infectious reactions in recipients

Certain regularity is the fact that the risk for transfusion-associated septic reactions is directly proportional to the duration and temperature at which blood and its components are stored. Some bacteria die or cannot proliferate in the temperature at which blood components are stored. Yet such cryophilic bacteria as *Yersinia enterocolitica* survive in red blood concentrates because low temperatures do not act destructively on them. Platelet concentrates, which are stored in room temperature, are a more friendly environment for

bacteria to survive and proliferate although some, more sensitive ones, die at 20 – 24^{0}C. Most Gram-positive and Gram-negative bacteria are able to survive and proliferate in platelet concentrates.

In most reported cases of transfusion-associated bacterial sepsis, the sources of blood component contaminations were not identified. Yet the type of bacteria responsible for the complications enabled the probable cause of sepsis and hypothetical source of pathogenic bacteria to be established. For example, coagulase-negative *Staphylococci* or *Corynebacteria* in platelet concentrates suggest the epidermal origin, but *Streptococcus viridans* in blood most likely originates from a donor undergoing dentistry procedures.

2.1 Bacterial infections transmitted with red blood cell concentrates

Red blood cell concentrate is a blood component, which is transfused most frequently. It does not contain only red blood cells but also various amounts of platelets and leukocytes. Transfusion-associated bacterial sepsis resulting from transfusing a bacterially contaminated red blood cell concentrate is rather uncommon. Different reports estimate its rate at 1:250,000 transfusions; the relevant sepsis mortality rate ranges 58 – 70% (5). During nine years, FDA registered 25 fatalities due to transfusion of contaminated red blood cell concentrate (6). Thus, the mortality risk is estimated at 13:1,000,000 red blood cell concentrate transfusions (7). On the other hand, the Dana Farber Cancer Institute studies have found the infection prevalence at 1:38,000 transfused red blood cell concentrate units (8,9).

The bacterium most commonly responsible for sepsis associated with red blood cell concentrate transfusion is *Yersinia enterocolitica*. The prevalence of sepsis associated with *Y. enterocolitica* transmitted with blood varies. In New Zealand, it is 1:65,000 transfusions, with the sepsis fatality rate estimated at 1:104,000 transfused red blood cell concentrate units (4). In USA, 20 cases were reported of *Yersinia* being transmitted with blood components in 1987 – 1996. Twelve of them died before the 37th day following the transfusion of contaminated red blood cell concentrate. The mean time between transfusion and recipient's death is 25 hours (10). *Yersinia enterocolitica* is a Gram-negative bacterium, responsible for diarrheal diseases; it may also temporarily colonize the alimentary tract of asymptomatic people. The feature characteristic of *Yersinia* bacteria is their ability to survive and proliferate in temperatures in which red blood cell concentrates are stored, i.e. +2 – +6 ^{o}C. For their own metabolism they also use citrate as the source of carbon, which is an additional factor conducive for bacterial proliferation. Citrate compounds are included in commonly used anticoagulants. *Yersinia* bacteria present in a blood component are a typical example of endogenous contamination resulting from asymptomatic donor's bacteremia. A study has shown that around 2/3 of donors, in whom *Yersinia enterocolitica* was detected, had complained of gastrointestinal disorders in the time preceding blood donation. Most often these ailments had a mild course (9,11,12,13,14). *Yersinia* may remain in the circulation, inside leukocytes, even for a few days after intestinal complaints subside. This bacterium is also resistant to the action of complement components and to phagocytosis due to the presence of Yersinia outer proteins (Yops) (15,16).

The likelihood of transmitting bacteria via red blood cell transfusion is directly associated with the duration of their storing. Tests of red blood cell concentrates that had been contaminated with *Yersinia* showed that in the 38th day after blood donation, the number of bacteria reached 10^8 - 10^9 CFU/ml. Between the 21st and 34th days, bacteria very quickly proliferated and released endotoxin, whose concentration reached around 315 μg/ml (17).

Except for *Yersinia enterocolitica*, the bacteria which may contaminate red blood cell concentrates and potentially cause an endotoxic shock, are *Pseudomonas* spp., *Serratia* spp., *Enterobacter* spp., *Campylobacter* spp. and *Escherichia coli* (15).

Pseudomonades are Gram-negative bacteria commonly found in water and soil. They can proliferate in temperature 4°C. They often contribute to red blood cell concentrate contamination during concentrate preparation (18). *Serratia marcescens* was a causative factor in transfusion-associated sepsis reported in Denmark and Sweden, where bacterially contaminated containers were used at blood donations (19).

Serratia is also a Gram-negative bacterium, which proliferates easily in poor environment at +4 – +22°C. The bacteria were isolated from both red blood cell concentrates and platelets concentrates. Transmitting *Serratia*, especially *Serratia liquefaciens*, causes transfusion-associate sepsis, most often fatal (1,20).

A prospective analysis of bacterial cultures from whole blood and red blood cell concentrates has shown that bacterial contamination is much more common in blood components, i.e. 2 – 4 per 4,000 units. The bacteria most often cultured were *Staphylococcus* and *Propionibacterium* spp. They very rarely cause sepsis in recipients because they do not proliferate at +2 – +6 °C, and red blood cells are stored just at this temperature range. Table 4 shows bacteria found in red blood cell concentrates.

Blood component	Bacteria	Prevalence of bacteria detected that caused complications
Red blood cell concentrate	*Yersinia enterocolitica* *Pseudomonas fluorescens* *Pseudomonas putida* *Treponema pallidum* Other bacteria	51.0% 26.5% 4.1% 4.1% 14.3%

Table 4. Bacteria detected in red blood cell concentrates

There have been also two fatal cases of transfusion-associated sepsis described caused by *Pantoeae agglomerans*, which used to be known as *Enterobacter agglomerans* (21). That bacterium possesses plasmid-associated factors, which make it resistant to phagocytosis (22,23).

Autologous blood is also a source of severe transfusion-associated sepsis. There are cases reported in the literature describing transmitting *Y.enterocolitica* infection following autologous transfusion (12,23). In Japanese studies, a common bacterium contaminating blood from autologous transfusions was coagulase-negative *Staphylococcus* (24,25).

2.2 Bacterial infections transmitted by contaminated platelet concentrate

The risk for being infected with bacteria in transfused platelets is 50 to 250 times higher than that associated with red blood cell transfusions (26).

In platelet concentrate transfusion-associated sepsis, bacteria belonging to the donor's skin flora are the main infectious factor. Thus, they are typical exogenous infections resulting from badly disinfected skin in the site of needle insertion. The bacteria most commonly contaminating platelet concentrates are *Staphylococcus epidermidis*, which constitutes over 50% of all bacteria detected and *Bacillus cereus*, which belong to the physiological skin flora (27,28). These bacteria do not proliferate at 0°C, but are able to proliferate in the temperature

at which platelets are stored, i.e. 20 – 24°C. If the course of the infection associated with platelet transfusion is rapid, mainly Gram-negative bacteria are to blame. There have been cases reported of fatal transfusion-associated sepsis caused by *Staphylococcus aureus* and *Clostridium perfringens*. The source of *Clostridium difficile* was a donor, who frequently changed nappies of his newborn baby. Platelet concentrates can also contain other *cocci*, *Corynebacterium pseudodiphtheriticum*, also Gram-negative fermentative bacteria of the *Pseudomonas* genus. Recently, *Listeria monocytogenes* was isolated from an apheresis platelet concentrate (29). Although there have been no cases reported of isolating *Listeria monocytogenes* from other blood components, it must be remembered that iron, which is present in blood, e.g. in red blood cells, is conductive to the growth and virulence of this bacterium T(29).

Most bacteria are able to proliferate at 20°C – 24°C, but different bacteria have different growth dynamicity. In the case of *S.aureus* and *Pseudomonas*, after the first two days they start proliferating very quickly, whereas *Enterococcus faecalis* typically grows slowly and steadily. Transfusion-associated sepsis has been reported following transfusing platelet concentrates contaminated with Gram-positive bacteria (30).

Sepsis caused by transfusing bacterially contaminated platelet concentrates is most common. Platelets are stored at room temperature and are a perfect medium for bacterial proliferation. The prevalence of symptomatic platelet transfusion-associated infections is 1:5,000 in the case of pooled concentrates, and the relevant mortality rate ranges from 1:70,000 to 1:100,000 transfusions (31,32). Table 5 shows bacteria most often detected in platelet concentrates.

Blood component	Bacteria	Prevalence of detected bacteria that caused complications
Platelet concentrate	*Staphylococcus epidermidis*	25 %
	Salmonella choleraesuis	13.5 %
	Serratia marcescens	9.6 %
	Staphylococcus aureus	9.6 %
	Bacillus cereus	3.8 %
	Streptococcus viridans	5.8 %
	Other bacteria	36.5 %

Table 5. Bacteria and their prevalence in platelet concentrates

Transfusion-associated bacterial sepsis usually manifests immediately after or still during transfusion. There have been seven cases reported of sepsis caused by *Salmonella* in platelet concentrate recipients, which manifested 5 – 12 days after transfusion (33). All the platelet units had been collected from the same donor who was later diagnosed with chronic ostitis.

Bacteria contaminating blood components can be neutralized by such bacteriostatic factors as complement and phagocytosing cells. Yet, for many bacterial types, a concentration as small as 1 CFU/ml may be sufficient to proliferate (34). After an initial 2 – 3 day latency phase, bacteria rapidly proliferate to reach a concentration of 10^8 – 10^9 CFU/ml in the 2nd – 5th day of storing.

Haemovigilance studies carried out in many countries focus on severe adverse transfusion-associated reactions caused by bacteria. Table 6 presents a summing-up of these studies.

Study	Time of study	Number of cases of blood component contamination	Kind of blood component	Number of deaths from transfusion-associated sepsis
SHOT	1996-1998	4	1 red blood cell concentrate 3 platelet concentrates	0 1
French Hemovigilance	1994-1999	185	113 red blood cell concentrates 89 platelet concentrates	8 10
Bacthem	1996-1998	41	25 red blood cell concentrates 16 platelet concentrates	6 2
BaCon	1998-2000	34	5 red blood cell concentrates 29 platelet concentrates	3 6

Table 6. Findings of studies on bacterial contamination of blood components (35)

The UK Serious Hazards of Transfusion (SHOT) study collects and analyzes all cases of transfusion-associated adverse reactions. In 1996 – 1998, there were 366 cases in all of adverse reactions registered within SHOT, four of which were transmitted by transfusing bacterial infection (36). Transfusion-associated sepsis developed after transfusing 1 unit of red blood cell concentrate contaminated with *Serratia liquefaciens* and three units of platelet concentrate which were contaminated with *Escherichia coli, Bacillus cereus* and *Staphylococcus aureus*. Transfusion-associated sepsis caused by *S.aureus* resulted in the patient's death (36).

In the French Hemovigilance Study carried out in 1994 – 1999, there were 730 transfusion-associated bacterial infection events, out of which 185 were qualified in the end (89 following red blood cell concentrate transfusions and 113 after platelet concentrate transfusions) (37). Eighteen recipients died after developing transfusion-associated bacterial sepsis. The risk for transfusion-associated bacterial reactions was estimated at 12.6:1,000,000 blood component units. Bacteria isolated from red blood cell concentrates were Gram-positive *cocci* (58%), mainly *Staphylococcus* spp and *Streptococcus* spp, and Gram-negative bacteria found in 32% of units. The both types of bacteria were found in 10% of cases. In platelet concentrates, Gram-negative bacteria were found in 36% of units, Gram-positive *cocci* in 42%, and other bacteria in 22% (37). Another French study (Bacthem) focused on years 1996 – 1998. During that time, there were 41 transfusion-associated cases analyzed. 25 cases following transfusing red blood cell concentrates (4 deaths) and 16 cases following transfusing platelet concentrates (2 deaths). The bacteria contaminating the red blood cell concentrates in that study were mainly Gram-negative (52%) in contrast to 37% detected in the platelet concentrates. The risk for transfusion-associated sepsis was three times higher when platelet concentrates were transfused and 12 times higher when transfusing pooled platelet concentrates. Moreover, the risk for transfusion-associated bacterial sepsis was

higher when platelets had been stored longer than 1 day, and red blood cells for longer than eight days (38). One of the conclusions drawn from the study was that there is a strict correlation between the kind of blood component, duration of storing it and the risk for transfusion-associated bacterial sepsis (38).

The American BaCon Study assessed the prevalence of transfusion-associated bacterial adverse reactions, kinds of bacterial contamination of blood components and risk factors for transfusion-associated bacterial sepsis occurrence. The study was conducted in 1998 – 2000 (7). In that time, 34 cases of bacterial adverse reactions were assessed, nine of which were fatal. As the cause of transfusion-associated sepsis, the following bacteria were identified – Gram-positive: *Staphylococcus epidermis* (8 cases), *S.aureus* (4 cases), and Gram-negative: *Escherichia coli* (5 cases) and five cases where *Serratia* were identified (3 – *S.marcescens*, 2 – *S.liquefasciens*) (7). The course of transfusion-associated bacterial sepsis was more rapid in patients who had been transfused blood components contaminated with Gram-negative bacteria than in those in whom the component transfused was contaminated with Gram-positive bacteria. The researchers showed that transfusion-associated bacterial sepsis was developed five times more often after pooled platelet concentrates were transfused than after transfusing platelets from aphaeresis. In the BaCon study, there were 4 deaths resultant from sepsis following transfusion of aphaeresis platelet concentrates, i.e from one donor, and two deaths after transfusing pooled platelet concentrates (7,39).

3. Sources of blood components bacterial contamination

The most probable sources of blood component bacterial contamination are donor's bacteremia, blood collection and processing procedures. Table 7 presents possible sources of bacterial contamination.

Contamination source	Contamination mechanism
Blood donor	Latent bacteremia Respiratory system flora Nasopharyngeal flora
Blood collection procedures	Normal skin flora Pathological, transient skin flora Practice of and equipment for blood collection
Blood processing procedures	Contaminated containers Open systems Infected enriching fluids

Table 7. Sources and mechanisms of bacterial contamination of blood components

Blood donors suffering from asymptomatic bacteremia or recovering from bacterial infections are a source of blood component bacterial contamination. *Yersinia enterocolitica*, a Gram-negative bacterium, can cause intestinitis with diarrhea of various intensity, increased temperature and abdominal pain. Yet, the infection is asymptomatic in most cases. Thus, such donors are a potential source of blood component contamination (40,41). Transfusion associated bacterial sepsis may be caused by other intestinal pathogens, such as *Campylobacter jejuni* and *Salmonella Heidelberg*, which induce donor's bacteremia (18). They damage the intestinal mucosa and move into blood. In some people, only after they donated

blood were internal latent foci of infection detected. They were asymptomatic, yet they caused low-level bacteremia. There have been cases reported of sepsis after transfusing concentrate of platelets taken from donors who were during the incubation of bacterial infections of the respiratory tract and endocarditis (41). A donor can develop a short-time bacteremia after dentistry procedures. *Staphylococcus aureus* was detected in a platelet concentrate collected from a donor two hours after his tooth was treated conservatively (18). *Staphylococcus aureus* is not the only bacterium that can be the source of blood component contamination. There have been two cases reported where bacterial toxins were detected in the bags after transfused platelet concentrates. Recipients of this component developed manifestations of septic shock 15 and 20 minutes after their respective transfusions were begun (42).

The procedures of collecting blood and its components are a source of platelet concentrate contamination mainly. Most bacteria detected in laboratory tests and reported as the cause of transfusion-associated sepsis are those which constitute the normal skin flora or those which transiently are present at the venopuncture site. An example of blood components being contaminated with bacteria that happened to be in the venopuncture site is a case of sepsis caused by *Salmonella enterica*. During an epidemiological investigation, it was found that the bacteria had originated form a platelet donor who had a snake. The bacteria were cultured from the recipient's blood, form the bag where the blood component had been stored and the snake's excrements, but *Salmonella enterica* was not cultured in the donor's blood. The bacteria, most probably, was on the donor's skin while platelet concentrate was collected by apheresis (43).

There are known cases of severe transfusion-associated bacterial sepsis caused by red blood cell concentrates contaminated with *Pseudomonas fluorescens* originating from swabs used as cooling compresses on the venopuncture site in donors with low pain tolerance (44).

Yet most blood components become contaminated because the venopuncture site has been disinfected insufficiently or because disinfectants were contaminated. There has been a case reported of red blood cell concentrate being contaminated with *Burkholderia cepacia*, because the chlorhexidine used for disinfecting the venopuncture was contaminated with this bacterium (45).

Since disposable, sterile closed plastic systems for blood collection, processing and storage were introduced, there have been very uncommon situations when lack of adequate sterilization of a blood collection kit or contamination during blood processing resulted in contaminating a blood component. A practically invisible crack in a bag for blood or blood components can result in their contamination (10).

4. Clinical picture

Diagnosing transfusion-associated bacterial sepsis is difficult when the diagnosis is to be based only on clinical manifestations. That is why the criteria to diagnose this complication have been worked out and are presented in Table 8 (4).

Transfusion-associated bacterial sepsis always manifests clinically in a very dramatic manner. The first symptoms (fever, shivering), which confirm the presence of bacteria in the recipient's circulation usually appear within 2 hours following the start of the transfusion. The symptoms to follow are blood pressure drop, nausea, vomiting, diarrhea, and shock. Other symptoms, such as dyspnea or bleeding, result from bacteria inducing endotoxins. Delayed manifestations, which appear later than one day after transfusion, have been

reported following transfusing bacterially contaminated platelet concentrates (46). Transfusion-associated bacterial sepsis diagnosed too late is the most common cause of death. Early symptoms of sepsis may be diagnosed as non-infectious transfusion-associated adverse reactions, especially in neoplastic disease patients under immunosuppression, who have undergone numerous blood component transfusions.

Within around 90 minutes after transfusion was started, one of the following symptoms appears:
1.   Fever ≥39°C or increase in body temperature by 2°C
2.   Shivering
3.   Tachycardia (≥120 beats per minute or increase by ≥40 bpm)
4.   Changes in systolic pressure (increase by ≥30 mmHg or decrease in comparison to baseline values)

Table 8. Criteria to diagnose transfusion-associated bacterial sepsis

The initial number of bacteria that is transfused in contaminated blood components is not large; it rarely exceeds 10 CFU/ml. That is why transfusing blood or its components within the first two days following donation is associated with a minimal risk for infectious transfusion-associated complications. Yet, a unique group of recipients constitute patients under immunosuppression, for whom even a very small number of bacteria are very dangerous. In most transfusion-associated bacterial reactions, the level of contamination in containers was at $10^6 – 10^8$ CFU/ml. Such levels were found in platelet concentrates stored for 3 – 5 days, and red blood cell concentrates stored for at least three weeks.

Severe sepsis with a rapid disease course is mostly caused by Gram-negative bacteria releasing an endotoxin which activates the immune system very strongly. Such bacteria are predominantly found in contaminated red blood cell concentrates and claim a very high mortality rate.

Bacterial endotoxins – lipopolysaccharide (LPS) – are in the Gram-negative bacterial cellular wall and penetrate the environment after a bacterium disintegrates, and in a small amount, when a bacterium proliferates because then its cellular wall becomes less dense. They stimulate macrophages to secrete such inflammatory cytokines as TNFα, IL-1ß, IL-6, IL-8, which are responsible for numerous systemic reactions associated with septic shock. Patients who had been transfused red blood cell concentrate contaminated with Gram-negative bacteria had high plasma concentrations of these cytokines. Septic shock observed in recipients of contaminated concentrates must have resulted mainly from a massive release of cytokines rather than from the bacterial proliferation in the recipient's organism (47).

Bacterial strains responsible for severe transfusion-associated reactions may have certain features, such as resistance to phagocytosis or ability to activate complement, which enable them to proliferate in blood components. Asymptomatic, Gram-negative bacteremia in a blood donor is a phenomenon that accompanies alimentary tract infections and alimentary toxicosis. In the case of intestinal motility disorders, bacteria that are present on the surface of mucosa are able to penetrate into deeper tissue and blood. Bacteremia resultant from translocation usually does not pose a serious threat to donors whose immune system functions normally. Bacteria are eliminated from the circulation and sepsis does not develop. On the other hand, the consequences of transfusing a bacterially contaminated blood component may be very severe when the number of bacteria is very large or the recipient is a patient with low immunity.

The mortality rate is high and depends on the blood component, kind and amount of contaminating bacteria and patient's clinical condition (including comorbidities). Other factors affecting the mortality rate are the ability to respond adequately to the infection and the kind of diagnostic and therapeutic procedures. Studies show that sepsis caused by transfusing contaminated red blood cell concentrates is particularly lethal (48). The factors that primarily negatively affect the defense against infections include chronic pulmonary diseases, neutropenia, immunosuppression, senility, and poor nutrition.

5. Differentiating

Differential diagnosis of transfusion-associated bacterial sepsis includes hemolytic reactions, febrile non-hemolytic reactions, TRALI, and sepsis unassociated with blood component transfusion. The diagnosis is based on culturing patient's blood and a unit of the component transfused. The bacterial background of the transfusion-associated reaction is confirmed when the same bacterium is cultured from a container with the blood component and from patient's blood. The similarity of the bacteria cultured from both sources is based on the bacterial DNA structure established with one of the methods for genetic typing (most often it is pulsed field gel electrophoresis – PFGE).

6. Treating transfusion-associated bacterial sepsis

The basic principles in treating transfusion-associated bacterial sepsis include early clinical suspicion, rigorous implementation of diagnostic procedures, appropriate causal therapy, inhibiting generalized inflammatory reactions predisposing to complications.

When a fast growing fever appears, the transfusion should be discontinued, the container with the accompanying drains secured, and a blood sample taken from the patient so that microbiological tests can be done. The blood sample for culturing should be taken from another vein than the one into which the blood component has been transfused.

Before microbiological tests findings are available, empiric therapy should be introduced. Antibiotic therapy should include such broad spectrum antibiotics as ß-lactams and aminoglycosides. When bacterially contaminated red blood cell concentrate transfusion-associated sepsis is suspected, an antibiotic with anti-*Pseudomonas* activity should be introduced. Then targeted antibiotic therapy should be started. When a septic shock occurs, shock-controlling procedures should include monitoring hemodynamics, respiratory efficiency and kidney function. In fluid resuscitation, crystalloids and natural or artificial colloid solutions are used. The first transfusion consists of 500 – 1000 ml of crystalloids or 300 – 500 ml of colloids during 30 minutes, and is repeated depending on such parameters as blood pressure, diuresis, and possibly volume overload.

7. Prevention

There are no absolutely reliable methods which can enable bacterial contamination of blood components to be detected effectively before transfusion. The methods used at present include four categories: (1) avoiding bacterial infections, (2) bacteriological testing of blood components, (3) inhibiting bacterial growth, and (4) techniques of pathogen inactivation.

A method to prevent platelet transfusion-associated bacterial sepsis may be using platelets from one donor collected by apheresis instead of pooled. The findings of a 12-year study,

where adverse septic reactions after platelet transfusions were analyzed, showed that an increase in transfusing apheresis platelet concentrates was accompanied by a decrease in such reactions (39). Other studies have confirmed these observations pointing to the fact that bacterial contamination of pooled red blood cell concentrates is higher than in those collected from one donor (40). Yet, the findings of another paper described more bacterial contaminations in apheresis concentrates (49).

7.1 Lowering the risk of donor's asymptomatic bacteremia
7.1.1 Avoiding bacterial infections

Most people infected develop clinical manifestations of infection, which naturally disqualifies them as blood donors. The problem appears when a donor has an asymptomatic infection with bacteria in blood or transient, asymptomatic, bacteremia, e.g. after dental treatment or some diagnostic procedures. A key prophylactic action is to perform a thorough epidemiologic interview in the form of a questionnaire. The questionnaire should cover the largest possible number of situations which carry the risk for infection contracting and transmitting. Yet, even a best designed questionnaire is not always able to detect asymptomatic bacteremia in a donor and to prevent transfusing contaminated blood. Studies performed by CDC (Centers for Disease Control and Prevention) have shown that out of 6,000 people asked if they had experienced any alimentary tract disorders in the previous 30 days, 13% answered positively (50). Other studies showed that 1/3 of the donors in whose blood *Yersinia enterocolitica* was found had not complained of any gastro-intestinal disorders (12).

7.1.2 Lowering the risk for contaminating collected blood with donor's skin flora

The skin is richly colonized with bacterial flora, which is present in the superficial layer, on the epidermis, and in the deeper layers colonizing sebaceous glands, sudoriferous glands, and hair follicles. Even when the venopuncture site is prepared properly, not always is it possible to avoid contaminating the blood collected with the skin flora. Contamination with coagulase-negative *Staphylococcus* species is very common. Another commensal bacterium prevalent in the deeper skin layers and frequently contaminating blood taken is *Propionibacterium*. It is a bacterium that grows slowly in a low-oxygen environment (10). A few studies have shown that blood collected became contaminated with such bacteria as *S.epidermidis*, *Pseudomonas fluorescens*, *Pseudomonas putida*, despite the fact that skin bacteriological cultures harvested from the venopuncture site were aseptic (10).

Skin disinfection at the venopuncture site is a specific way to prevent blood contamination; what is particularly important is not only using proper disinfectants but mainly disinfecting correctly and making sure the duration of particular stages of the disinfection process (time when a disinfectant is active) is as it should be.

A venopuncture site is disinfected most effectively with iodine solutions. Yet, a large number of skin allergic reactions have resulted in iodine being replaced by chlorhexidine and isopropyl alcohol (51,52). Table 9 presents the effectiveness of different disinfectants.

There should be at least two stages in the disinfection procedure with disinfectants whose manufacturers recommend the contact with the skin must be at least 30 seconds long. In practice, this means disinfectants must be used in the same manner they are used during preparations to surgery.

What significantly diminishes the risk for contaminating collected blood with a donor's skin flora is diversing the initial aliquot (around 20 – 30 ml) of the blood taken. This blood is used

for standard laboratory tests. Some authors claim such a practice may reduce the initial amount of bacteria in the blood taken even by 70 – 90%, but it does not eliminate the risk for its being contaminated (53,54,55).

Number of bacterial colonies / dish	Povidone iodine (% donors)	Isopropyl alcohol and iodine solution (% donors)	Chlorhexidine (% donors)	Green soap and isopropyl alcohol (% donors)
0 1 – 10 12 – 100 > 100 P (compared to povidone)	34 – 49% 35 – 43% 10 – 14% 0 – 13%	63% 34% 2% 1% < 0.001	60% 25% 12% 3% > 0.001	0% 17% 47% 36% < 0.001

Table 9. Comparison of disinfectants efficacy (Goldman et al.) (46)

7.2 Bacteriological testing of blood components

Blood components are always tested bacteriologically in two situations:
1. During an epidemiologic investigation; when sepsis signs occurred in a recipient during or after transfusion and it is suspected that an infectious agent has been transfused;
2. Randomly, as a control study within the prophylaxis against transfusion-associated adverse reactions.

The presence of bacteria in blood and its components can be detected with methods that are fast but not sensitive and have low specificity, e.g. macroscopic assessment, pH measurement, glucose concentration; or by using methods much more sensitive and specific, but requiring special equipment and highly qualified personnel. Table 10 presents different methods used to detect bacteria in blood components.

1. Macroscopic assessment of blood components a) Red blood cell concentrate changes color b) Hemolisis in red blood cell concentrate c) Swirling phenomenon assessment in platelet concentrate 2. Microscopic assessment of blood and its components (Gram staining, fluorescence microscopy) 3. Measuring glucose concentration, pCO_2, pO_2 and pH while blood components are being stored 4. Detecting bacteria endotoxins 5. Microbiological testing 6. Detecting bacterial genetic material 7. Using flow cytometry to detect bacteria

Table 10. Methods used to detect bacteria in blood components

In bacterially contaminated red blood cell concentrates, some features of red blood cells are changed. While blood components were being assessed macroscopically, hemolisis and a

dark color have been observed in the concentrate with high levels of *Yersinia enterocolitica*, *Enterobacter* spp. and other Gram-negative bacteria (56,57,58). This phenomenon may result from bacteria using up the oxygen bound with hemoglobin in red blood cells. In contaminated blood components, methemoglobin concentration was found to be 2 – 4 times higher than in "healthy" components. In bacterially contaminated red blood cell concentrates, pH was found to be lower.

Similar changes have been observed in platelet concentrates. Bacterial proliferation uses up glucose in the environment and, consequently, lowers pH (58). Oxygen concentration is observed to decrease and that of CO_2 to increase (35,58). Yet, changes in these parameters do not necessarily mean there are bacteria present, because leukocytes and platelets also take up glucose and oxygen form the environment. The metabolism of platelets in stored concentrates is very vivid. That is why simple and direct measurement of these parameters does not indicate unambiguously bacteria are present. The sensitivity of the macroscopic assessment of blood components is around 10^8 CFU/ml. One of the studies on bacterial contamination of blood components showed the method was more sensitive. Bacterial contamination of $1.8x10^4$ to $1.6x10^9$ CFU/ml was found in the whole blood which earlier at macroscopic assessment was suspected of being contaminated (57).

In bacterially contaminated platelet concentrates, the "swirling" phenomenon is observed, i.e. platelet blinking or twinkling. When platelets are seen in a light beam going through blood, they swirl and reflect light and thus the swirling phenomenon is produced. This phenomenon disappears or is attenuated when there are bacteria in platelet concentrate, which lower pH (35).

Blood components are assessed microscopically for detecting bacteria in both red blood cell concentrates and platelet concentrates. The assessment is based on Gram staining. Unfortunately, this method's sensitivity is very low. It is possible to detect bacteria when their concentration is $10^5 – 10^6$ CFU/ml (59). When the two methods of detecting bacteria in blood were compared (culturing on bacteriological medium and microscopic assessment), more than half of the samples where bacteria were cultured were negative microscopically (60). The use of acridine orange to detect bacteria in blood components has also been reported (61).

Genetic methods, which detect bacterial genetic material, are of a very high sensitivity. Methods based on the polymerase chain reaction (PCR) detect the genetic material of *S.aureus*, *E.coli*, *B.cereus* and *K.pneumoniae* in platelet concentrates with the sensitivity of 10 CFU/container (62). Other genetic methods use probes directed at a precisely defined bacterial DNA fragment, mainly 16SrDNA. They enable many different bacteria to be detected in blood components (63). The presence of marked probes is detected with chemiluminescence or electroluminescence. The test lasts a few hours, so theoretically it might be performed before each transfusion, and then the duration of storing blood components could be more "flexible" (10). The advantage of genetic methods is their speed and high sensitivity. Their disadvantage is the fact that they detect bacteria both alive and non-viable.

Flow cytometry is a method of the speed and sensitivity similar to those of genetic methods. Moreover, it differentiates bacteria which are alive from those which are dead.

At present, bacteria in blood components can be detected routinely with the method of marking them with fluorescence dyes and found on a special membrane (after filtration). The principle of this method is used in an automatic system where bacteria can be detected within 30 – 72 hours since blood collection. The time of the test is short, around 90 minutes, and detects bacterial contamination at 105 CFU/ml (64).

The present "gold standard" in detecting bacteria in blood and its components is considered to be a method based on measuring CO_2 concentration in a bag with biological medium with an appropriate amount of the platelet concentrate tested. An increase in pCO_2 is detected (as a marker of bacterial presence) by the calorimetric index (10).

None of the methods described above is able to detect bacterial contamination of blood components if its concentration is very low. Donor's subclinical bacteremia in its initial phase has bacterial concentration at ≤10 CFU/ml and is undetectable. That is why blood components are tested for bacterial contamination 24 hours after blood was collected. Although this practice delays obtaining the result of the test, it allows the cause of the contamination to be found and transfusion-associated bacterial sepsis to be avoided. Because of an increased risk for platelet concentrate transfusion-associated adverse reactions, in March 2004 FDA ruled that in the USA all platelet concentrates which are to be transfused have to be tested first (65). Similar regulations are in effect in some European countries.

7.3 Modifying the conditions of storing blood components

Platelet concentrate is a blood component in which bacteria have good conditions to survive. Lowering the temperature at which platelet concentrate is stored would inhibit bacterial proliferation and reduce the risk for transfusion-associated sepsis (4 – 6°C), but it would also affect negatively platelet haemostatic features and their survival in the circulation. This mechanism became known only recently (66). Short-time exposure of platelets to cold results in platelets clustering glycosylated protein GP1B on the surface of the chilled platelets. The aggregation process is induced by the binding of glycoprotein with receptors on macrophages, which immobilizes platelets. The phenomenon is transitional if platelets are not stored in the cold for longer than two hours. If platelet concentrate is stored in the cold for longer than 48 hours, platelet functions are distorted by competitive blockade of the asialo receptors, which results in platelet survival time in the circulation becoming shorter (66). Routinely, platelet concentrates are stored at 20 – 24 °C for up to 5 days, but after each unit is tested bacteriologically, the storing period may be prolonged to 7 days. There are opinions heard universally that the present guidelines should be changed and the duration of blood component storage should be shortened (10).

Most severe cases of transfusion-associated bacterial sepsis have been reported after transfusing red blood cell concentrates stored for over 2 weeks, because at the temperature of 2 – 6°C bacterial growth and metabolism are either inhibited or considerably slower. The temperature of 4°C does not stop *Yersinia*, *Pseudomonas* and *Serratia* from growing. A few centers have introduced "a preceding period" to red blood cell concentrate storage. The idea was to leave red blood cells in room temperature for 5 – 7 hours, and then perform a bacteriological test. It turned out that a longer time of incubation (about 7 hours) at room temperature improved detection of *Yersinia enterocolitica*, whereas such bacteria as *Enterococcus* or *Klebsiella* were much more numerous after 4 hours of incubation (67,68).

The temperature of 2 to 6°C is an inhibiting factor not only for bacteria. Cellular activity and the activity of immune system factors in fresh blood are inhibited too. That is why it is beneficial to leave the blood collected at room temperature for 2 – 4 hours so that natural mechanisms could act and destroy bacteria (12).

7.4 Inactivation of bacteria contaminating blood components

The techniques used to reduce bacteria contaminating blood components are new methods able to limit the risk for transfusion-associated bacterial sepsis. These methods are effective

both when well-known infectious agents are encountered and also when the agents have so far been neglected from the transfusiology point of view, or even those which have not been discovered yet. They should possess the following features:

- They should inactivate a broad spectrum of bacteria;
- They should not change the therapeutic properties of a blood component;
- Reagents and photoproducts, whose traces may remain after the reduction process is finished, must not be toxic to recipients;
- The costs of implementation should be proportional to their effectiveness (69,70)

The effectiveness assessment is based on comparing the number of model bacteria added to blood components before and after inactivation. The method is believed to be effective if the number of bacteria is diminished by 5 – 6 $\log_{10}$ in reference to the baseline values (71, 72).

In *in vitro* studies, the parameter defining the effectiveness of the method is the reduction index (R), which is a negative logarithm (Y) of the ratio between the number of bacteria in the baseline material to the number of bacteria after reduction plus/minus 1:

$$R = - \log (Y) \pm 1$$

The reduction index is dependent on many factors. The most important are: baseline bacterial concentration, their type and kind of blood component.

Naturally, it is not enough to establish that a particular method of pathogen reduction is effective. It is necessary to carry out *in vitro* tests of particular blood components before and after reduction (69). Such tests aim to establish to what extent blood components change their functional and metabolic properties during storing. The methods of bacterial reduction must not distort biochemical metabolic transformations of red blood cells and platelets. If a method is to be applied clinically, a blood component after pathogen reduction with a particular method should be safe, therapeutically effective and must not cause adverse reactions (69).

The methods used in order to limit transmitting bacteria by contaminated blood components can be divided into two groups. In the first group, there are those procedures which inactivate bacteria. Inactivation destroys their capsules or damages their DNA/RNA, which prevents their proliferation. One of such methods is the Solvent/detergent method used mainly to reduce pathogens in the capsule.

The second group of methods focuses on eliminating the infectious factor completely or on lowering its amount so that it would not be infectious any longer. They are methods of photoinactivation with visual or UV radiation and such radiosensitive compounds as psolarens, as well as filtration. They are used to reduce pathogens in platelet and red blood cell concentrates (73).

The methods of inactivation with riboflavin are being clinically tested. The methods used for red blood cell concentrates must not need light exposure because light is absorbed by hemoglobin.

Clinical tests in the form of transfusing platelet concentrates inactivated with psolarens have shown lack of toxicity and their photoproducts. Photoinactivation with psolarens proves to be an effective method that inactivates a broad spectrum of both Gram-negative and Gram-positive bacteria. Platelets inactivated in this way have been proved sterile for the whole time of storage and the metabolic functions of these blood cells were preserved even in the 7th day of storing. Yet, what has to be considered as negative is an approximate 10% loss in the number of platelets after the process of inactivation (71).

The methods of pathogen reduction in blood components have been recommended as priorities to be applied and further studied so that the safety of blood and its components will improve (74,75).

Filtration, used to limit bacterial contamination in blood components, results in the removal of leukocytes together with bacteria inside them. Bacteria may adhere to leukocytes on the filter too. Free forms of bacteria can be also removed by direct adhesion to the filter material. Several *in vitro* studies have shown that filters which reduce the number of leukocytes are able to rid contaminated red blood cell concentrates or whole blood of bacteria (38,49,76). The blood units, into which *Y.enterocolitica* bacteria were added a few hours after collection, and which underwent filtering so that leukocytes would be removed, contained fewer bacteria than those which had not been filtered. On the other hand, diminishing the number of leukocytes by filtering them out is less effective in removing bacteria from platelet concentrates (76). The number of bacteria grew slower in low-leukocyte platelet concentrates, but after one day the concentration of bacteria contaminating this blood component did not differ significantly from others. Similarly, molecular studies of bacterial RNA showed the same growth rate of bacteria in platelet concentrates contaminated with *S.epidermidis* (77). Filters which reduce the number of leukocytes can catch bacteria directly, which is illustrated by the fact that *Staphylococcus xylosus* can be removed from blood components which were filtered previously (77). Yet, other studies have proved that filtering blood is able to reduce the number of bacteria in blood components, but it is never able to filter out the contamination fully (78). Filtering out leukocytes from blood components can also eliminate phagocytized bacteria inside them (76). If granulocytes disintegrate before bacteria are destroyed, they can get into the blood again. The optimal time to perform filtration is probably 2 to 12 hours following blood collection. It is the time for phagocytosis and reduction of leukocytes before viable bacteria are released from them (77). This mechanism has been used to explain why bacteria are found in the blood components which were previously considered uncontaminated. The interests of the haemovigilance study program included the benefits resulting from leukocyte reduction in blood components. The results revealed that the percentage of bacterially contaminated blood components had been considerably lowered (3.8% before filtering vs 1.7% after filtering) and the number of transfusion-associated bacterial sepsis cases significantly reduced (71% vs 24%) (54).

8. Summing-up

Bacterial contamination of blood components is a cause of transfusion-associated sepsis. The components which most often become contaminated are those of red blood cells and of platelets. Blood components often become bacterially infected during blood collection from a donor; more seldom in the case of asymptomatic bacteremia or faulty blood processing. The methods used currently, which are based on culturing, visual assessment of a component, appropriate selection of donors, venopuncture site disinfection techniques, more often than not are able to prevent transfusion-associated bacterial sepsis. The techniques of pathogen inactivation may turn out to be promising in preventing bacterial infections.

9. References

[1] Brecher ME., Hay SN.: Bacterial contamination of blood components. Clin Microbiol Rev 2005;18:195-204.

[2] Goldman M., Lee JH., Blajchman M.: Skin antisepsis and initial aliquot diversion. In Brecher ME. (ed): Bacterial and parasitic contamination of blood components. Bethesda, AABB Press 2003:31-56.

[3] Seghatchian J.: Bacterial contamination of blood components. Transfus Apher Sci 2001;25:147-150.

[4] Hillyer CD., Josephson CD., Blachman MA. et al: Bacterial contamination of blood components: risks, strategies, and regulation. Hematology 2003;1:575-589.

[5] Blajchman MA., Backers EAM., Dickmeiss E. et al: Bacterial detection of platelets: Current problems and possible resolutions. Transfus Med Rev 2005;19:259-272.

[6] Niu MT., Knippen M., Simmons L. et al: Transfusion-transmitted *Klebsiella pneumonia* fatalities, 1995 to 2004. Transfus Med Rev 2006;20:49-57.

[7] Kuchnert MJ., Roth VR., Haley NR. et al: Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. Transfusion 2001;41:1493-1499.

[8] Barrett BB., Anderson JW., Anderson KC.: Strategies for the avoidance of bacterial contamination of blood components. Transfusion 1993;33:228-233.

[9] Dzieczkowski JS., Barret BB., Nester D. et al: Characterization of reactions after exclusive transfusion of white cell-reduced cellular blood components. Transfusion 1995;35:20-25.

[10] Park YA., Brecher ME.: Bacterial contamination of Blood Products. In: Simon TL., Snyder L., Sdheim BG. et al (eds) Rossi's Principles of Transfusion Medicine. Bethesda, MD: AABB Press, 2009:773-790

[11] Benavides S., Nicol K., Koranyi K. et al: *Yersinia* septic shock following an autologous transfusion in a paediatric patient. Transfus Apher Sci 2003;28:19-23.

[12] US Dept. of Health and Human Services. Red blood cell transfusions contaminated with *Yersinia enterocolitica* – United States, 1991-1996 and initiation of a national study to detect bacteria-associated transfusion reactions. MMWR Morb Mortal Whly Rep 1997;46:553-555.

[13] Theakston EP., Morris AJ., Streat SJ. et al: Transfusion transmitted *Yersinia enterocolitica* infection in New Zealand. Aust NZ J Med 1997;127:62-67.

[14] Beresford AM.: Transfusion reaction due to *Yersinia enterocolitica* and review of other reported cases. Pathology 1995;27:133-135.

[15] Yomtovian R., Palavecino E.: Bacterial contamination of blood components: History and epidemiology. In: Brecher ME, et al: Bacterial and parasitic contamination of blood components. Bethesda, MD: AABB Press, 2003:1-30.

[16] Leclercg A., Martin L., Vergues ML. et al: Fatal *Yersinia enterocolitica* biotype 4 serovar 0:3 sepsis after red blood cell transfusion. Transfusion 2005;45:814-818.

[17] Arduino MJ., Bland LA., Tipple MA. et al: Growth and endotoxin production of *Yersinia enterocolitica* and *Enterobacter agglomerans* in packed erythrocytes. J Clin Microbiol 1989;27:1483-1485.

[18] Ramirez-Arcos S., Goldman M., Blajchman MA.: Bacterial contamination. In: Popovsky MA (ed): Transfusion Reactions AABB Press, Bethesda. MD. 2007:163-206.

[19] Heltberg O., Show F., Gerner-Smidt P. et. al: Nosocomial epidemic of *Serratia marcescens* septicaemia ascribed to contaminated blood transfusion bags. Transfusion 1993;33:221-227.

[20] Roth VR., Arduino MJ., Nobiletti SC. et al: Transfusion -related sepsis due to *Serratia liquefaciens* in the United States. Transfusion 2000;40:931-935.

[21] Benfell C: Unusual bacteria blamed for blood transfusion death. Circulator 2004; Fall: 2 [http://chapters.redeross.org/ca/norcal/phys/pdf/Cireulator_Oct2004.pdf].

[22] Gibb AP., Martin KM., Davidson GA. et al: Modeling the growth of *Yersinia enterocolitica* in donated blood. Transfusion 1994;34:304-310.

[23] Högman CF., Engstrand L.: Factors affecting growth of *Yersinia enterocolitica* in cellular blood products. Transfus Med Rev 1996;10:259-275.

[24] Richard C., Kolinas J., Trinidade CD.: Autologous transfusion – transmission of Yersinia – enterocolitica. JAMA 1992;268:1541-1542.

[25] Sugai Y., Sugai K., Fuse A.: Current status of bacterial contamination of autologous blood for transfusion. Transfusion Apheresis Sci 2001;24:255-259.

[26] Depcik-Smith ND., Hay SM., Brecher ME: Bacterial contamination of blood products: factors, options, and insights. J Clin Apheresis 2001;16:192-201.

[27] Klein HG.,Dodd RY., Ness PM. et al: Current status of microbial contamination of blood complements: Summary of a conference. Transfusion 1997;37:95-101.

[28] Halpin TJ., Kilker S., Epstein J. et al: Bacterial contamination of platelet pools-Ohio, 1991. MMWR Morb Mortal Whly Rep 1992;41:36-37.

[29] Guevara RE., Tormey MP., Nguyen DM. et al.: *Listeria monocytogenes* in platelets: A case report. Transfusion 2006;46:305-309.

[30] Holness L., Jones P., Knippen M. et al: 19-year review of fatalities due to contaminated blood and blood components. FDA Science, 2006 [http:// www.cfsan.fola.gov/~frf/forum06].

[31] Benjamin RJ., Mintz PD.: Bacterial detection and extended platelet storage: The next step forward. Transfusion 2005;45:1832-1835.

[32] Fang CT., Chambers LA., Kennedy J. et al: Detection of bacterial contamination in apheresis platelet products: American Red Cross experience, 2004. Transfusion 2005;45:1845-1852.

[33] Rhame FS., Root RK., MacLowry JD. et. al: Salmonella septicaemia from platelet transfusions: Study of an outbreak traced to a hematogeneous carrier of *Salmonella choleraesius*. Ann Intern Med 1973;78:633-641.

[34] Wagner SJ., Moroff G., Katz AJ. et al.: Comparison of bacteria growth in single and pooled platelet concentrates after deliberate inoculation and storage. Transfusion 1995;35:298-302.

[35] Smith LA., Wright-Kanuth MS.: Bacterial contamination of blood components. Clin Lab Scien 2003;16:230-239.

[36] Williamson LM., Lowe S., Lowe EM. et al.: Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. BMJ 1999;319:16-19.

[37] Andren G., Morel P., Forestier F. et al.: Hemovigilance network in France: organization and analysis of immediate transfusion incident reports from 1994 to 1998. Transfusion 2002;42:1356-1364.

[38] Perez P., Salmi LR., Follea G. et al: Determinants of transfusion-associated bacterial contamination: results of the French BACTHEM case-control study. Transfusion 2001;41:862-872.

[39] Ness P., Braine H., King K. et al.: Single-donor platelets reduce the risk of septic platelet transfusion reaction. Transfusion 2001;41:857-861.

[40] Brecher ME., Holland PU., Pineda AA. et al.: Growth of bacteria in inoculated platelets: implications for bacteria detection and the extension of platelet storage. Transfusion 2000;40:1308-1312.

[41] Engelfriet CP., Reesink HW., Blajchman MA. et al: Bacterial contamination of blood components. Vox Sang 2000;78:59-67.

[42] 42. Perpoint T., Lina G., Poyart C. et al.: Two cases of fatal shock after transfusion of platelets contaminated by *Staphylococcus aureus*: Role of superantigenic toxins. Clin Infect Dis 2004;39: e106-109.

[43] 43. Jafari M., Forsberg J., Gilcher RO. et al.: Salmonella sepsis caused by a platelet transfusion from a donor with a pet snake. N Engl J Med 2002;347:1075-1078.

[44] 44. Chaffin DJ: *Pseudomonas fluorescens*-related septic transfusion reaction resulting from contaminated cold cloths (abstract). Transfusion 2002;42:41S.

[45] 45. Garcia-Free JA., Grasa JM., Solano VM. Et al.: Bacterial contamination of blood components due to *Burkholderia cepacie* contamination of chlorhexidine battles. Vox Sang 2002;81:70-71.

[46] 46. Goldman M., Blajchman MA.: Blood product associated bacterial sepsis. Transfus Med Rev 1991;5:73-83.

[47] 47. Robertson D., Davenport MD.: Management of Transfusion Reactions. In: Mintz PD. (ed): Transfusion Therapy Clinical Principles and Practice. AABB Press, Bethesda, Maryland 2005;526-528.

[48] 48. Walther-Wenke G.: Incidence of bacterial transfusion and transfusion reactions by blood components. Clin Chem Lab Med 2008;46:919.

[49] 49. Goldman M., Sher G., Blajchman M.: Bacterial contamination of cellular blood products: the Canadian perspective. Transfusion Sci 2000;23:17-19.

[50] Grossman BJ., Kollins P., Lan PM., et al: Screening blood donors for gastrointestinal illness. A strategy to eliminate carriers of *Yersinia enterocolitica*. Transfusion 1991;31:500-501.

[51] Mc Donald CP., Lowe P., Roy A. et al: Evaluation of donor arm disinfection techniques. Vox Sang 2001;80:135-141.

[52] Goldman M., Roy G., Frechette N. et al: Evaluation of donor skin disinfection methods. Transfusion 1997;37:309-312.

[53] Bruneau C., Perez P., Chassaingue M. et al: Efficacy of a new collection procedure for preventing bacterial contamination of whole-blood donations. Transfusion 2001;41:74-81.

[54] De Korte D., Marcellis JH., Verhoeven AJ. et al: Diversion of first blood volume results in a reduction of bacterial contamination for whole-blood collection. Vox Sang 2002;83:13-16.

[55] Eder AF., Kennedy JM., Dy BA. et al.: Limiting and detecting bacterial contamination of apheresis platelets: inlet-line diversion and increased culture volume improve component safety. Transfusion 2009;49:1554-1563.

[56] Bradley RM., Gander RM., Patel SK. et al: Inhibitory effect of 0ºC storage on the proliferation of *Yersinia enterocolitica* in donated blood. Transfusion 1992;37:691-695.

[57] Pichard C., Herschel L., Seery P. et al: Visual identification of bacterially contaminated red blood cells (abstract). Transfusion 1998;38 :125.

[58] Brecher ME., Foster M., Mair D.: Glucose and haemolysis as a rapid screen for contamination of red blood cells with Yersinia and Serratia. Vox Sang 2001;81:126-138.

[59] Kim DM., Brecher ME., Bland LA. et al: Visual identification of bacterially contaminated red cells. Transfusion 1992;32:221-225.

[60] Barrett BB., Anderson JW., Anderson KC.: Strategies for the avoidance of bacterial contamination of blood components. Transfusion 1993;33:228-233.

[61] Kim DM. Brecher ME., Bland LA. et al: Prostorage removal of *Yersinia enterocolitica* from red cells with white cell-reduction filters. Transfusion 1992;32:658-662.

[62] Schmidt M., Hourfar MK., Nico SB. et al: A comparison of three rapid bacterial detection methods under simulated real-life conditions. Transfusion 2006;46:1367-1373.

[63] Mohammadi T., Pietersz ANI., Vandenbroucke-Granls C. et al: Detection of bacteria in platelet concentrates: Comparison of broad-range real-time 16S rDNA polymerase chain reaction and automated culturing. Transfusion 2005;45:731-736.

[64] Brecher ME., Wong ECC., Chen SE. et al.: Antibiotic-labeled probes and microvolume fluorimetry for the rapid detection of bacterial contamination in platelet components: a preliminary report. Transfusion 2000;40:411-413.

[65] Silva MA. (ed).: Standards for blood banks and transfusiology. AABB Press. Bethesda, MD:2006.

[66] Rumjantseva V., Grewal PK., Wandall HH. et al.: Dual roles for hepatic lectin receptors in the clearance of chilled platelets. Nat Med 2009;15:1273-80.

[67] Weinberg JA., Mc Gwin G.Jr, Margues MB. et al.: Transfusion in the less severely injured: does age of transfused blood affect autcomes ? J Trauma 2008;65:794-798.

[68] Rawn J.: The silent risks of blood transfusion. Curr Opin Anaesthesiol 2008;21:664-668.

[69] Solheim BG.: Pathogen reduction of blood components. Transfus Apher Sci 2008;39:75-82.

[70] Solheim BG., Flesland O., Seghatchian J. et al.: Clinical implications of red blood cell and platelet storage lesions: an overview. Transfus Apher Sci 2004;31:185-189.

[71] Lin L., Dikeman R., Molini B. et. al: Photochemical treatment of platelet concentrates with amotosalen and long-wavelength ultraviolet light inactivates a broad spectrum of pathogenic bacteria. Transfusion 2004;44:1496-1504.

[72] Ruane PH., Edrich R., Grampp D. et al.: Photochemical inactivation of selected viruses and bacteria in platelet concentrates using riboflavin and light. Transfusion 2004;44:877-885.

[73] Pelletier JP., Tramsue S., Snyder EL.: Pathogen inactivation techniques. Best Pract Res Clin Haematol 2006;19:205-242.

[74] 96th Blood Products Advisory Committee Meeting, November 2009. Available at: http://www.fda.gov/AdvisoryCommitteeMeetingMaterials/BloodVaccinesandOt herBiologics/default.htm. AccessedMarch 17,2010.

[75] Klein HG., Glynn SA., Ness PM. et al.: Research opportunities for pathogen reduction / inactivation of blood components: summary of an NHLBI workshop. Transfusion 2009;49:1262-1268.

[76] Siblini L., Lafenillade B., Ros A. et al.: Reduction of *Yersinia enterocolitica* load in deliberately inoculated blood: the effects of blood prestorage temperature and WBC filtration. Transfusion 2002;42:422-427.

[77] Miller JP.: Leucocyte-Reduced and Cytomegalovirus-Reduced Risk Blood Components. In: Mintz PD. (ed): Transfusion Therapy Clinical Principles and Practice. AABB Press, Bethesda MD, 2005:541-578.

[78] Holden F., Foley M., Devin G. et al.: Coagulase-negative staphylococcal contamination of whole blood and its components: the effects of WBC reduction. Transfusion 2000;40:1508-1513.
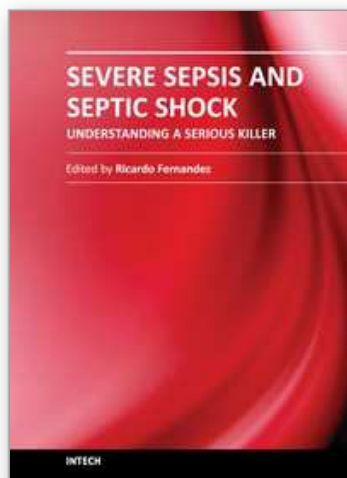
Severe Sepsis and Septic Shock - Understanding a Serious Killer

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Despite recent advances in the management of severe sepsis and septic shock, this condition continues to be the leading cause of death worldwide. Some experts usually consider sepsis as one of the most challenging syndromes because of its multiple presentations and the variety of its complications. Various investigators from all over the world got their chance in this book to provide important information regarding this deadly disease . We hope that the efforts of these investigators will result in a useful way to continue with intense work and interest for the care of our patients.

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