I controlli di sterilità degli emocomponenti: l'esperienza del Policlinico di Milano

Sterility testing of blood components: the experience of the Policlinico of Milan

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FONDAZIONE IRCCS CA' GRANDA OSPEDALE MAGGIORE POLICLINICO

MILANO, ITALY

Centro Trasfusionale,
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano

Siamo un servizio di Medicina Trasfusionale ad elevata complessità.

- Attività assistenziali e cliniche:
  - 35.000 donazioni per anno (circa 27.000 donatori attivi)
  - Sede di uno dei 9 Centri di Lavorazione e Validazione della Lombardia e del DMTE Milano centro
  - 50.000 emocomponenti lavorati distribuiti per anno (Policlinico + 10 ospedali convenzionati)
  - Banca regionale del sangue raro (5000 donazioni tipizzate per anno) e laboratorio di immunoematologia diagnostica (riferimento nazionale)
  - Ambulatori di Ematologia della gravidanza, e prevenzione della malattia emolitica neonatale
  - Unità di aferesi terapeutica (raccolta staminali, plasma exchange, fotoaferesi (circa 300 procedure per anno) e laboratorio di manipolazione cellulare
  - Banca del sangue cordonale (10.000 unità, quasi 1/3 di tutte le unità conservate in Italia)
  - Banca di microbiota intestinale (inizio 2018)
  - Unità di medicina traslazionale / cell factory
- Ricerca:
  - Biobanca POLI-MI(100.000 campioni)
  - Attualmente più di 15 progetti di ricerca con finanziamento
  - Nuovi progetti soprattutto basati su omics, medicina personalizzata ed exome sequencing, a sostegno delle numerose attività di ricerca traslazionale in corso (immunoematologia, studio delle melattie metaboliche nei donatori di sangue, terapie cellulari)

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Outline

- Blood components for transfusion
- Cord blood units
- Platelet gel & autologous eye drops
- ATMPs

Sterility testing: approaches in Milan

- ***Quality control (+ passive surveillance)*** → **% testing**

  "Conventional" blood components
  - Platelet transfusion
  - Red cell transfusion

- ***Active surveillance*** → **screening**

  Blood components for non-transfusion use, cell therapies
  - Platelet gel & eye drops
  - Cord blood units
  - Hematopoietic stem cell units (from BM and peripheral blood)
  - Advanced therapy medicinal products (ATMPs), from cell factory

Outline

- Blood components for transfusion
- Cord blood units
- Platelet gel & autologous eye drops
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- "**La qualità degli emocomponenti** deve essere garantita attraverso l'esecuzione di specifici controlli, pianificati per quantità e frequenza sulla base di adeguate valutazioni statistiche (**controllo statistico di processo**), al fine di ottenere dati statisticamente rappresentativi rispetto al volume complessivo della produzione dei singoli emocomponenti".

ISBT Science Series
An affiliated publication to Vox Sanguinis
ISBT International Society of Blood Transfusion
ISBT Science Series (2014) 9, 148–154

STATE OF THE ART 2C-S05-01

A fresh look at measuring quality in blood components

D. V. Devine & D. Chen
Centre for Innovation, Canadian Blood Services, and Centre for Blood Research, University of British Columbia, Vancouver, BC, Canada

Table 2 Canadian standards for blood products

Component	Test	Sample type	Frequency	Specification
Pooled platelets	Platelet yield	Unit	1% or min 10/month	$>2{\cdot}4 \times 10^{11}$ in at least 75%
	pH	Unit	1% or min 10/month	6·4–7·8 in at least 95%
	Residual leucocyte count	Aliquot	1% or min 10/month	$<5 \times 10^{6}$ in 100%
	Sterility	Unit	1% or min 10/month	No growth in all
Apheresis platelets	Platelet yield	Segment	1% or min 10/month	$>3 \times 10^{11}$ in at least 75%
	pH	Unit	1% or min 10/month	6·4–7·8 in at least 95%
	Residual leucocyte count	Segment	1% or min 10/month	$<5 \times 10^{6}$ in 100%
	Sterility	Unit	1% or min 10/month	No growth in all
Frozen plasma	Factor VIII	Unit	1% or min 10/month	≥0·52 IU/ml in 75%
	Volume	Unit	1% or min 10/month	±10%, ≥100 ml in 100%
Cryoprecipitate	Fibrinogen	Unit	1% or min 10/month	>150 mg/unit in 75%
	Volume	Unit	1% or min 10/month	5–15 ml in 100%
Cryosupernatant	Volume	Unit	1% or min 10/month	±10%, ≥100 ml in 100%
	Factor VIII	Segment	1% or min 10/month	≥0·70 IU/ml in 75%
Fresh frozen plasma, apheresis	Sterility	Aliquot or Unit	1 component/machine (1–100 components) 2 components/machine (101–200 components)	No growth in 100%
SAGM RBC, LR	Haemoglobin	Unit	1% or min 10/month	≥40 g/unit in 90% ≥35 g/unit in 100%
	Haemolysis	Unit	1% or min 10/month	<0·8% in 100%
	Residual leucocyte count	Segment	1% or min 10/month	$<5 \times 10^{6}$ in 100%
	Sterility	Unit	1% or min 10/month	No growth in 100%

Anno 2016 : Dati di produzione CLV Regione Lombardia Questionario

N° unità prodotte CP da Pool di BC: 43843

(In 8 CLV da 5 buffy-coat, in 1 CLV da 4 buffy-coat)

214.442 (Buffy-Coat utilizzati)

- **Controlli di sterilità**
- **Controlli di qualità Wbc residui dopo leucodeplezione**
- **Controlli di qualità della Concentrazione PLT**
- **Controlli di qualità del volume**

Metodiche di preparazione, Metodiche dei CQ, n° campionamenti

Coordinatore: Dr. Luca Stocco, Lecco

Emocomponente: CP Pool da BC
Parametro: Controllo di Sterilità
Periodo analisi: Anno 2016
Standard Rif Racc R(95) 15: Esito Coltura Negativo

Calcolo delle prevalenze attese dei prodotti non Conformi

Controllo di sterilità	CLV 1	CLV 2	CLV 3	CLV 4	CLV 5	CLV 6	CLV 7	CLV 8	CLV 9	Lombardia
Produzione annua	6173	1307	3792	4788	1705	5795	8519	6991	4773	43843
n	**166**	**51**	**78**	**12**	**89**	**100**	**98**		**8**	**602**
Media (μ)										
DS (σ)										
NC	**1**	**0**	**0**	**0**	**0**	**0**	**0**		**0**	**1**
% NC	**0,6%**	**0,0%**	**0,0%**	**0,0%**	**0,0%**	**0,0%**	**0,0%**	**#DIV/0!**	**0,0%**	**0,2%**
p	0,0060240964	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	#DIV/0!	0,0000000000	0,0016611296
1 - p	0,9939759036	1,0000000000	1,0000000000	1,0000000000	1,0000000000	1,0000000000	1,0000000000	#DIV/0!	1,0000000000	0,9983388704
Varianza di p	0,0000360711	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	#DIV/0!	0,0000000000	0,0000027548
Errore Standard	0,0060059241	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	#DIV/0!	0,0000000000	0,0016597493
Errore Standard %	0,60%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	#DIV/0!	0,00%	0,17%
1,96*P	0,01177161	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	#DIV/0!	0,00000000	0,00325311
P+	0,01779571	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	#DIV/0!	0,00000000	0,00491424
P-	-0,00574751	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	0,00000000	#DIV/0!	0,00000000	-0,00159198
I.C. 95% (+)	1,78%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	#DIV/0!	0,00%	0,49%
I.C. 95% (-)	-0,57%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	#DIV/0!	0,00%	-0,16%
$1,96^2$ (IC 95%)	3,8416	3,8416	3,8416	3,8416	3,8416	3,8416	3,8416	3,8416	3,8416	3,8416
(Prevalenza attesa) $P_{att\ Max}$	0,0177957076	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	0,0000000000	#DIV/0!	0,0000000000	0,0049142382
1 - P_{att}	0,9822042924	1,0000000000	1,0000000000	1,0000000000	1,0000000000	1,0000000000	1,0000000000	#DIV/0!	1,0000000000	0,9950857618
Precisione desiderata (5%) D^2	0,0025	0,0025	0,0025	0,0025	0,0025	0,0025	0,0025	0,0025	0,0025	0,0025
Numerosità del campione	**26,86**	**0,00**	**0,00**	**0,00**	**0,00**	**0,00**	**0,00**	**#DIV/0!**	**0,00**	**7,51**
Prevalenza attesa IC 95 %	**0 - 1,78%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**		**0%**	**0 - 0,49%**

Coordinatore: Dr. Luca Stocco, Lecco

Sterility testing,
blood components for transfusion
data at Policlinico di Milano

	Data per year			
Blood component	**N. Prepared**	**Microbial testing target % (*)**	**Microbial testing target N. (*)**	**Detected positive total N. (2013-2018)**
RBC	~40,000	0.5 %	~200	0
PLT	~5,500	1 %(°)	~55	0

(*) - From 2018 (previously data were scattered)

(°) - Percentage will be further increased in 2019

Microbial testing is done by Bactalert , 3-5 ml for aerobe, 10 ml for anaereobe
(units towards the end of shelf-life)

Is the 1% quality control sample adequate to assess bacterial safety of platelet concentrates?

Preparation size	Context	N. PLTs year	N. Tested	N. positive	Percent (95% CI)*
Larger	Whole region	50,000	500	1	0.2% (0.0%-0.6%)
Smaller	Center *x*	5,000	50	1	2% (0.0%- **5.3%**)
Smaller	Center *y*	5,000	50	0	0 (0.0% - **5.8%**)

- It is enough for assessing quality standards of higher numbers ; i.e. to assess if the preparation of platelet concentrates is under control at regional level.

- It is not adequate for single centers with lower preparation size; upper bound indicates that the possible frequency of contaminated blood products would be exceedingly high (up to 50-60 per 1,000) , even if all quality control runs are negative.

(*) Expected frequency : 0.05%-0.5% (UpTodate 2019)

Outline

- Blood components for transfusion
- Cord blood units
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Sterility testing

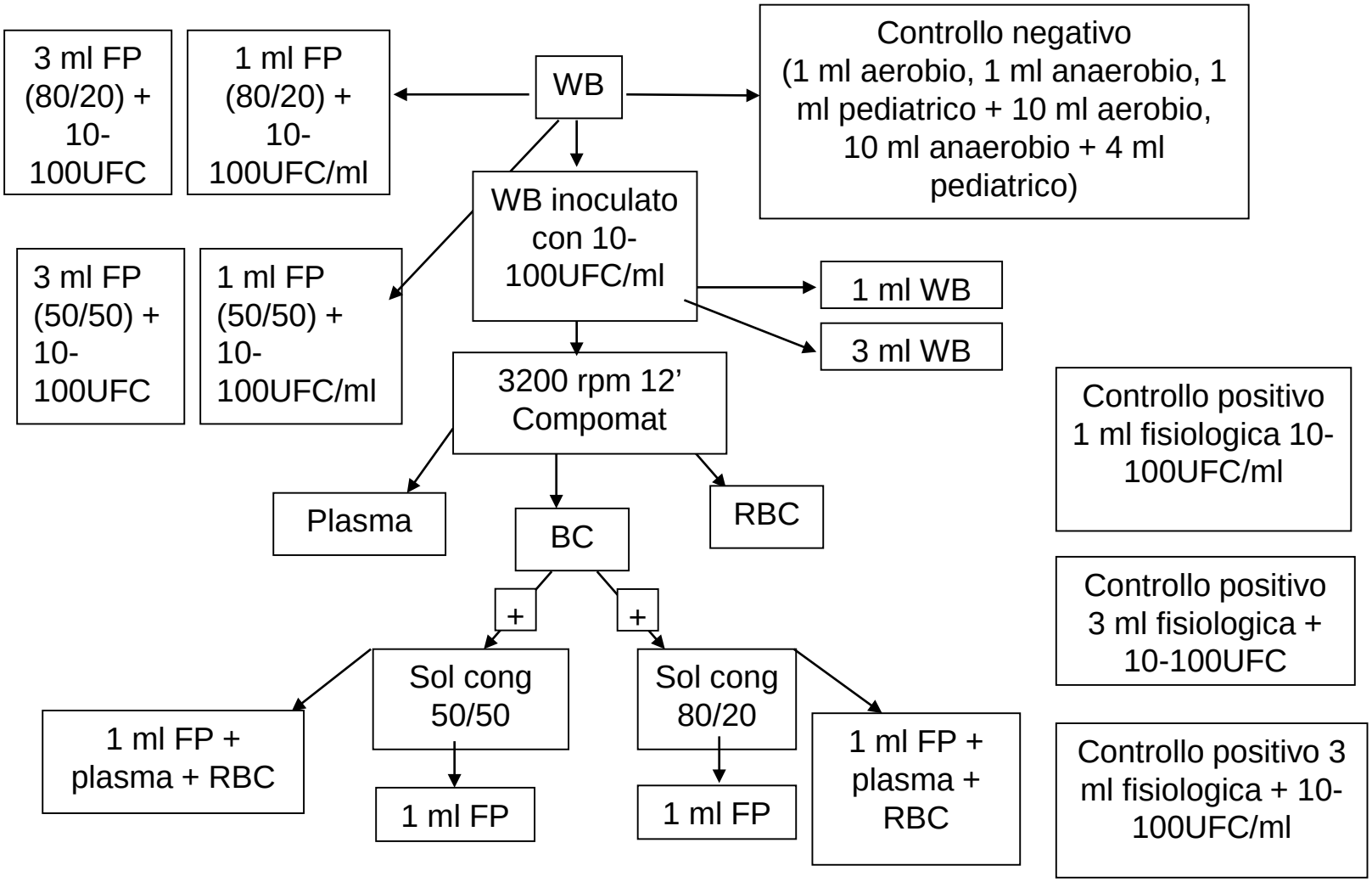
INTERNATIONAL STANDARDS FOR CORD BLOOD COLLECTION, BANKING, AND RELEASE FOR ADMINISTRATION *Sixth Edition*

- C6.3.3 CB. Collection procedures shall be validated to result in acceptable progenitor cell viability, cell recovery, and rate of microbial contamination.
- D9.3.2 Microbial cultures shall be performed using a system validated for the growth of aerobic and anaerobic bacteria and fungi.
- D9.3.2.1 Cord blood units for unrelated use shall be free from microbial contamination.
- D9.3.2.2 For related cord blood units, the results of positive microbial tests shall include identity and sensitivities of the organism(s). These results shall be reported to the prospective Clinical Program.

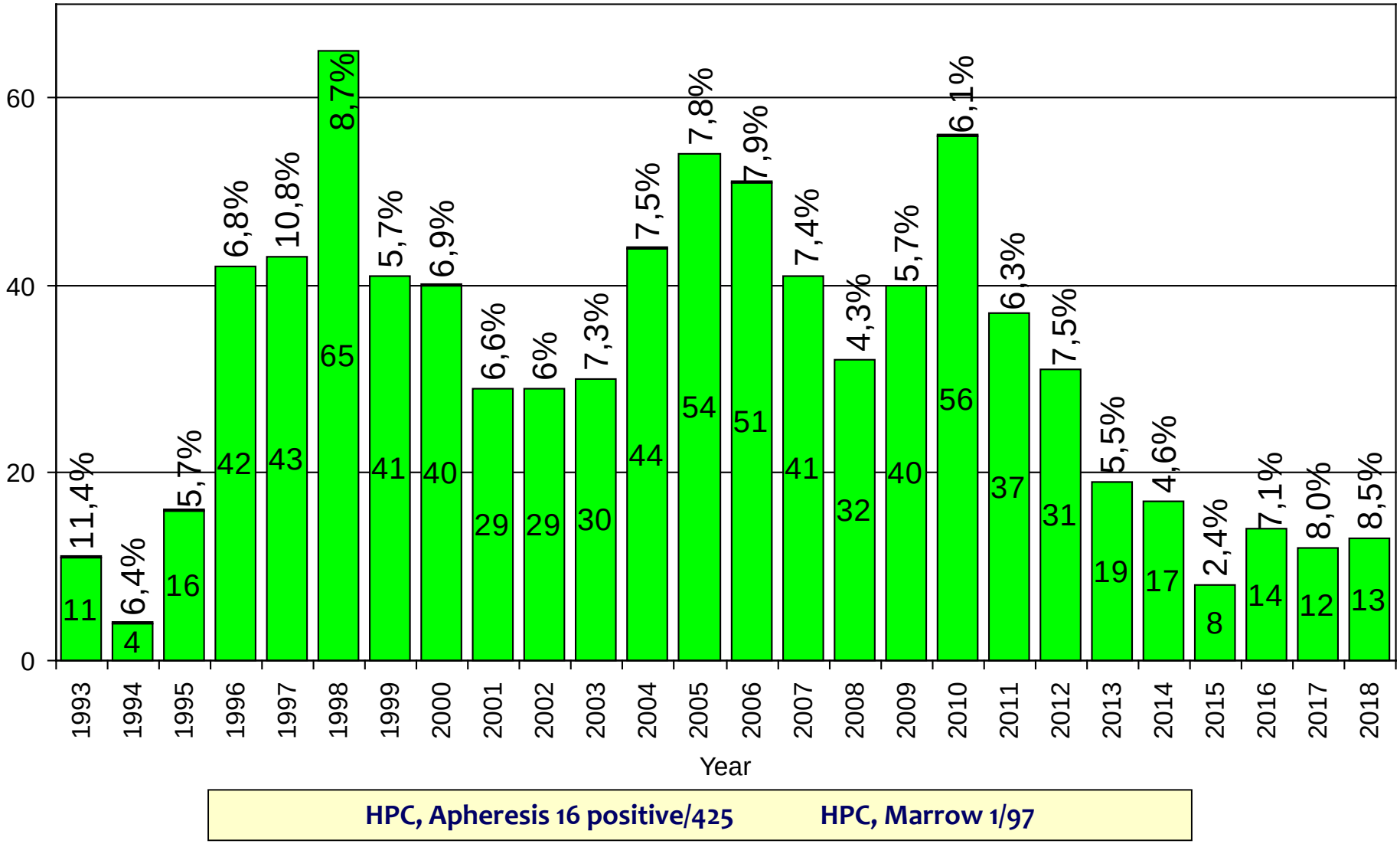
At Milano Cord Blood Bank

- Reagents evaluation for microbial contamination before implementation in routine use
- Test performed on the final product after addition of cryopreservation solution before freezing
- Requirements for unrelated cord blood units. Microbial Screen: Negative for aerobes, anaerobes, fungi
- Requirements for related cord blood units. Microbial Screen: Negative for aerobic and anaerobic bacteria and fungi – OR – identify and provide results of antibiotic sensitivities
- Unrelated cord blood units positive for microbial contamination are discarded
- Stability program. Monthly: microbial contamination on a thawed unit

Validation


3 ml FP (80/20) + 10-100UFC
1 ml FP (80/20) + 10-100UFC/ml
WB
Controllo negativo (1 ml aerobio, 1 ml anaerobio, 1 ml pediatrico + 10 ml aerobio, 10 ml anaerobio + 4 ml pediatrico)
WB inoculato con 10-100UFC/ml
3 ml FP (50/50) + 10-100UFC
1 ml FP (50/50) + 10-100UFC/ml
1 ml WB
3 ml WB
3200 rpm 12' Compomat
Plasma
BC
RBC
+
+
Sol cong 50/50
Sol cong 80/20
1 ml FP + plasma + RBC
1 ml FP
1 ml FP
1 ml FP + plasma + RBC
Controllo positivo 1 ml fisiologica 10-100UFC/ml
Controllo positivo 3 ml fisiologica + 10-100UFC
Controllo positivo 3 ml fisiologica + 10-100UFC/ml

Milano Cord Blood Bank - Sterility testing
Unrelated and related cord blood units with positive results. N=819 6,8%



HPC, Apheresis 16 positive/425 **HPC, Marrow 1/97**

Aerobic bacteria

Staphylococcus epidermidis	47
Streptococcus agalactiae	20
Enterococcus faecalis	18
Escherichia coli	18
POSITIVE	13
Corynebacterium spp	11
Staphylococcus hominis	8
Enterococcus faecium	7
Enterococcus species	6
Bastoncini gram positivi	5
Staphylococcus coagulase neg.	5
Staphylococcus haemolyticus	5
Staphylococcus capitis	4
Streptococcus alfa emoliticus	4
Bifidobacterium species	3
Micrococcus luteus	3
Staphylococcus lugdunensis	3
Bacillus spp.	2
Bacteroides spp.	2
Citrobacter freundii	2
Corynebacterium minutissimum	2
Flora mista	2
Klebsiella pneumoniae	2
Lactobacillus sp	2
Pseudomonas species	2

Staphylococcus cohnii	2
Staphylococcus warneri	2
Streptococcus bovis	2
Streptococcus gallolyticus	2
Streptococcus milleri	2
Acinetobacter baumannii	1
Acinetobecter lwoffii	1
Arcanobacterium haemolyticum	1
Bacteroides thetaiotaomicron	1
Bacteroides vulgatus - Clostridium innocuum	1
Bastoncini gram negativi	1
Brevibacterium sp	1
Burkholderia cepacia	1
Candida albicans	1
Cellulomonas spp	1
Clostridium ramosum	1
Corynebacterium Jeiekeium	1
Corynebacterium aquaticum	1
Corynebacterium group	1
Corynebacterium species	1
Corynebacterium striatum	1
Coryneform Gram positive rods	1
Enterobacter aerogenes	1
Enterobacter agglomerans	1

Enterobacter cloacae	1
Enterococcus casseliflavus	1
Enterococcus durans	1
Eubacterium limosum	1
Flavimonas oryzihabitans	1
Neisseria subflava	1
Oligella spp, Corynebacterium spp	1
Propionebacterium sp.	1
Propionibacterium acnes	1
Proteus mirabilis	1
Proteus vulgaris	1
Pseudomonas fluorescens	1
Pseudomonas putida	1
Ralstonia pickettii	1
Rod shaped Gram positive bacteria	1
Staphylococcus xylosus	1
Streptococcus anginosus	1
Streptococcus faecalis	1
Streptococcus pasteurianus	1
Streptococcus sanguis	1
Streptococcus species	1
Veillonella parvula	1

Anaerobic bacteria

Bacteroides vulgatus	87
Staphylococcus epidermidis	82
Bacteroides spp.	69
Escherichia coli	34
Bacteroides distasonis	30
Streptococcus agalactiae	28
Enterococcus faecalis	21
Bacteroides fragilis	19
Prevotella sp	19
POSITIVE	18
Enterococcus species	14
Bacteroides capillosus	13
Bacteroides ovatus	11
Flora mista	11
Peptostreptococcus spp.	11
Bastoncini gram positivi	10
Bifidobacterium spp	10
Bacteroides uniformis	9
Corynebacterium spp	8
Enterococcus faecium	8
Staphylococcus hominis	7
Prevotella bivia	6
Prevotella oralis	6
Propionibacterium acnes	6
Staphylococcus capitis	6

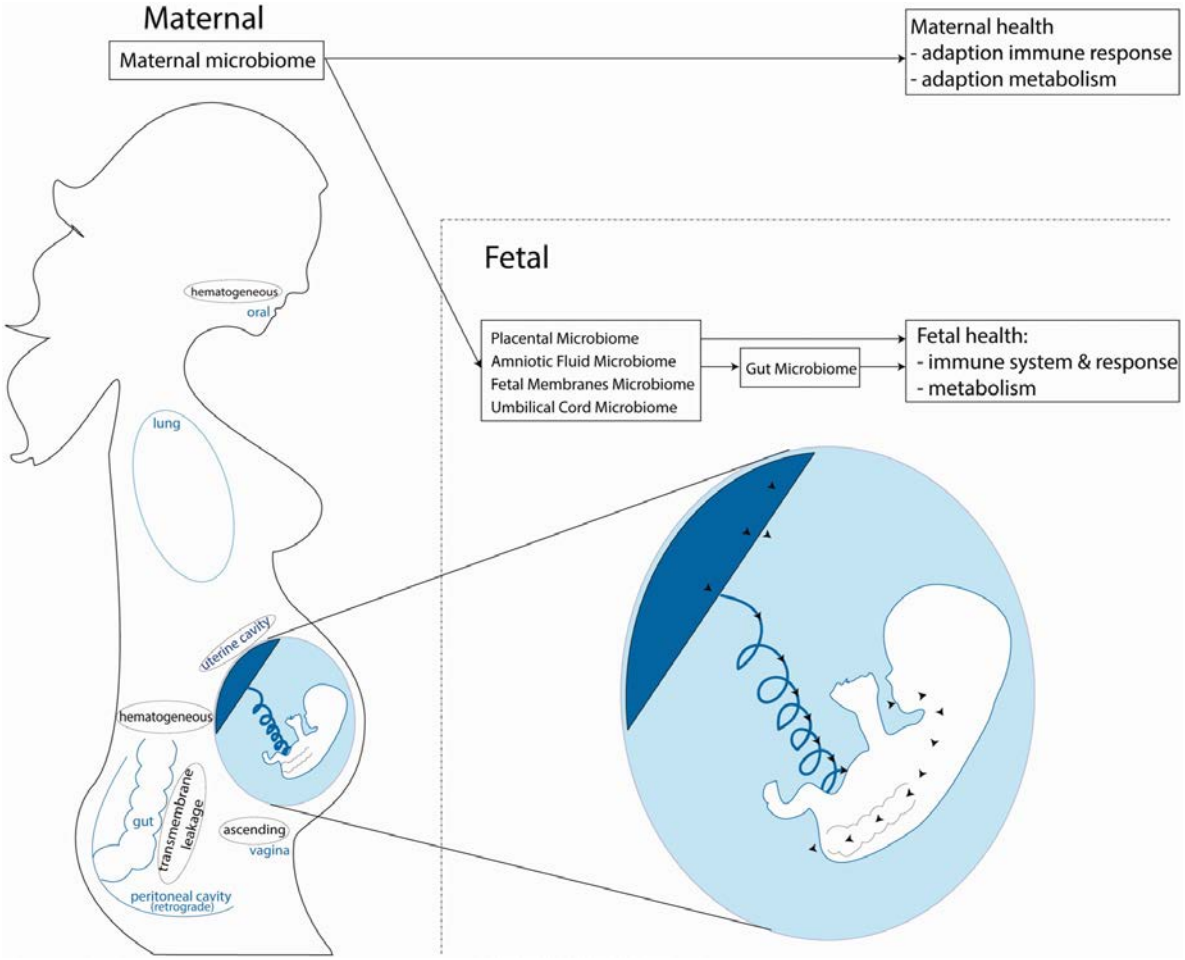
Staphylococcus haemolyticus	6
Eubacterium lentum	5
Peptostreptococcus asaccharolyticus	5
Prevotella disiens	5
Prevotella melaninogenica	5
Staphylococcus lugdunensis	5
Bacillus spp.	4
Bacteroides ureolyticus	4
Enterococcus durans	4
Peptostreptococcus anaerobius	4
Porphyromonas spp.	4
Prevotella oris	4
Staphylococcus warneri	4
Streptococcus gallolyticus	4
Bacteroides stercoris	3
Bastoncini gram negativi	3
Brevibacterium sp	3
Cellulomonas spp	3
Citrobacter freundii	3
Lactobacillus sp	3
Propionebacterium sp	3
Proteus mirabilis	3
Streptococcus anginosus	3
Streptococcus salivarius	3

Bastoncini gram + non sporigeni	2
Eubacterium limosum	2
Klebsiella pneumoniae	2
Porphyromonas gingivalis	2
Prevotella buccae	2
Staphylococcus coagulase neg.	2
Staphylococcus saprophyticus	2
Streptococcus bovis	2
Streptococcus milleri	2
Streptococcus species	2
Actinomyces israeli	1
Actinomyces odontolyticus	1
Aerococcus urinae	1
Anaerococcus prevotii	1
Bacillum gram-positive	1
Bacillus mycoides	1
Bacillus stearothermophilus	1
Bacteroides caccae	1
Bacteroides eggerthii	1
Bacteroides vulgatus - Clostridium innocuum	1
Bifidobacterium adolescentis	1
Bifidobacterium species	1
Citrobacter amalonaticus	1

Cord blood stability program. Monthly: microbial contamination on a thawed unit

Microbial test results according to delivery mode in cord blood units at MICB (1993-2019)

Delivery mode	Total N.	N. Positive	Percent Positive (95% CI)
Vaginal	8187	709	8.7 (8.1-9.3)
Cesarean	3125	45	1.4 (1.0-1.9)
Overall	11,312	754	6.6 (6.14-7.06)



DOI: (10.1177/1753495X18775899)

Baby's first bacteria

THE WOMB WAS THOUGHT TO BE STERILE. SOME SCIENTISTS ARGUE IT'S WHERE THE MICROBIOME BEGINS.

Isolation of Commensal Bacteria from Umbilical Cord Blood of Healthy Neonates Born by Cesarean Section

Esther Jiménez,[1] Leonides Fernández,[1] María L. Marín,[1] Rocío Martín,[1] Juan M. Odriozola,[2] Carmen Nueno-Palop,[3] Arjan Narbad,[3] Mónica Olivares,[4] Jordi Xaus,[4] Juan M. Rodríguez[1]

Current Microbiology Vol. 51 (2005), pp. 270–274

MMWR / December 21, 2018 / Vol. 67 / No. 50

Notes from the Field

Infections After Receipt of Bacterially Contaminated Umbilical Cord Blood–Derived Stem Cell Products for Other Than Hematopoietic or Immunologic Reconstitution — United States, 2018

Kiran M. Perkins, MD[1]; Samantha Spoto, MSPH[2]; Danielle A. Rankin, MPH[2]; Nychie Q. Dotson, MPH[2]; Mary Malarkey[3]; Melissa Mendoza, JD[3]; Lorrie McNeill[3]; Paige Gable[1]; Krista M. Powell, MD[1]

- On September 22, the Florida Department of Health received notification of Escherichia coli, Enterococcus faecalis, and Proteus mirabilis joint infections in four patients who had received injections of these same products at an orthopedic clinic during February 15– August 30, 2018, for other than hematopoietic or immunologic reconstitution (i.e., pain or orthopedic conditions)
- As of December 14, CDC has received reports of infections in 12 patients from three states.
- **The only approved use for cord blood derived stem cells is hematopoietic and immunologic reconstitution**

Outline

- Blood components for transfusion
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Sterility testing,
platelet gel & autologous eye drops
data at Policlinico di Milano in 2018

Blood component	Origin	N. Prepared	Microbial testing target %	Detected positive total N.	Percent positive (95% CI)
Platelet gel	Cord blood	264	100 %	7	2.7%(*) (1.1%-5.4%)
Eye drops	Autologous serum	129	100 %	3	2.3% (0.5%-6.6%)

(*) Since June 2019, CB-derived platelet gel will undergo two microbial checks: one on whole blood, one on the final product.

Microbial testing is done by Bactalert , 3-5 ml for aerobe, 10 ml for anaereobe
Positive units are discarded

Outline

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STERILITY TEST for ATMPs - (GMP compliance)

Advanced Therapy Medicinal Products (ATMPs)

Gene Therapies, Cell Therapies, Tissue Engineering

ATMP Manufacturing under **Good Manufacturing Practices** (GMP)= Subjected to standardized quality system

SAFETY AND EFFICACY

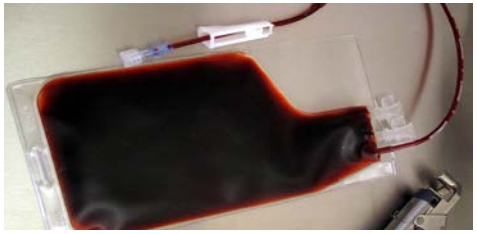
DETERMINE THE FREEDOM FROM ADVENTITIOUS AGENTS: bacteria, fungi, mycoplasma, viruses

STERILITY AS….

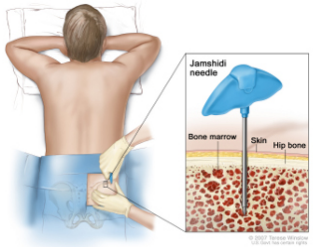
CELL FACTORY

STERILTY TEST ON RAW MATERIAL and INTERMEDIATE PRODUCTS

RAW MATERIALS



CORD BLOOD



BONE MARROW

ADIPOSE TISSUE

Intermediate PRODUCTTS

TEST METHOD:

BacT/AlerT 3D culture system

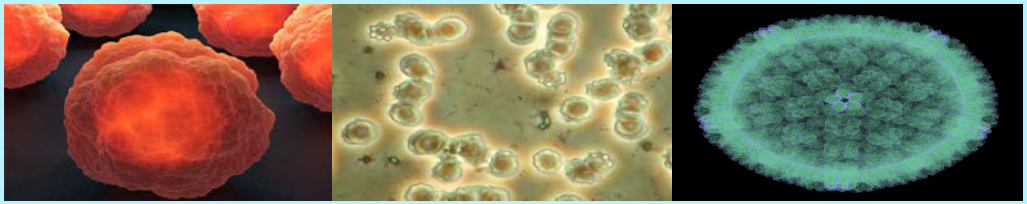
Automated non-destructive and non-invasive culture system that continuously monitors the culture of bacteria (both aerobic and anaerobic), fungi and mycobacteria. All these microorganisms can be cultured using the prescribed different media.

CELL FACTORY

STERILTY TEST ON FINAL PRODUCTS

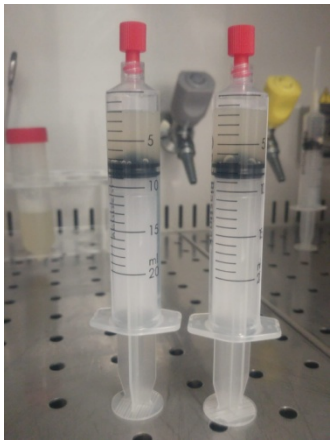
Sterility for..	Test method
Microbial contamination	Automatic method: BacT/AlerT 3D culture system
Bacterial endotoxins	Gel clot - limit test
Mycoplasma	Culture method
Adventious viruses (Respiratory viruses-CMV-EBV)	Molecular biology techniques (PCR)

FREEDOM



FROM ADVENTITIUOUS AGENTS

RELEASE of the cellular product



CELL FACTORY

Cell Factory STERILTY TEST

Sterility for..	Number of tests performed in 2015-2019
Microbial contamination	N= 417
Bacterial endotoxins	N= 51
Mycoplasma	N= 90
Adventious viruses (Respiratory viruses-CMV-EBV)	N= 52

Positive result for microbial contamination n=1/417 (in a process validation RUN)

OOS investigation, microbial strain identification (Staphylococcus Epidermidis)

In compliance with GMP rules, all the sterility tests have been validated according to the suitability method described in European Pharmacopeia.

Drug Design, Development and Therapy — Dovepress

METHODOLOGY

How we make cell therapy in Italy

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Abstract: In the 21st century scenario, new therapeutic tools are needed to take up the social and medical challenge posed by the more and more frequent degenerative disorders and by the aging of population. The recent category of advanced therapy medicinal products has been created to comprise cellular, gene therapy, and tissue engineered products, as a new class of drugs. Their manufacture requires the same pharmaceutical framework as for conventional drugs and this means that industrial, large-scale manufacturing process has to be adapted to the peculiar characteristics of cell-containing products. Our hospital took up the challenge of this new path in the early 2000s; and herein we describe the approach we followed to set up a pharmaceutical-grade facility in a public hospital context, with the aim to share the solutions we found to make cell therapy compliant with the requirements for the production and the quality control of a high-standard medicinal product.

Keywords: advanced therapy medicinal product, good manufacturing practices, stem cells

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Tips and Tricks for Validation of Quality Control Analytical Methods in Good Manufacturing Practice Mesenchymal Stromal Cell Production

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CELL FACTORY

Summary

- The approach to sterility testing for blood components, especially platelets, merit to be reconsidered (i.e., increasing the percentage of tested units? Shifting from quality control to 100% screening?).
- We already use a 100% screening approach for other preparations (cord blood, blood components for non transfusion use, cell factory products).
- Our cord blood sterility data cover more than 25 years and represents one of the largest series worldwide. The rate of positive microbial tests is around 6.5%. Infection may occur during delivery, but also be the result of a physiological mechanism which implies that the maternal micriobiome to reach and cross the placenta.
- Caution should be paid when cord blood derived cells are used outside hematopoietic cell transplantation programs.

Blood Components Unit

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- *Elisa Erba*
- *Laura Bava*

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