Cours de sciences de base

Département Anesthésiologie

Université de Montréal

Pharmacologie

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Pourquoi les cours de sciences de base en pharmacologie?

Il y a deux types de clinicien:
Celui qui base sa pratique sur les résultats des études prospectives randomisées
et
Celui qui se base sur son **interprétation** des résultats des études prospectives randomisées selon **ses connaissances en physiologie et pharmacologie.**

Can Ince, Bruxelles, mars 2013

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EVIDENCE BASED

et

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EVIDENCE BASED^{PLUS}

Can Ince, Bruxelles, mars 2013

Devrait-on utiliser un parachute lorsque l'on saute d'un avion?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

BMJ: Dec 2003

Gordon C S Smith, Jill P Pell

- Méta-analyse respectant les lignes directrices de QUORUM
- Point d'aboutissement primaire: prévention de la mortalité ou des traumas majeurs (Score > 15) par le parachute lors d'une **chute supérieure à 100 m.**
- Pas de RCT

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

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Des données observationnelles indiquent que l'utilisation du parachute est associée dans certains cas à la mort et les traumas majeurs surtout lors de mal fonctionnement et complications iatrogéniques.

Quelques histoires de cas nous indique que la chute libre sans parachute n'est pas inévitablement relié à la mort ou un trauma majeur.

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PARACHUTE ou CHUTE LIBRE de façon aléatoire

PARACHUTE

Thérapie de remplacement volémique

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

Ryan Zarychanski, MD, MSc
Ahmed M. Abou-Setta, MD, PhD
Alexis F. Turgeon, MD, MSc
Brett L. Houston, BSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Fergusson, PhD, MHA

Conclusion and Relevance In critically ill patients requiring acute volume resuscitation, use of hydroxyethyl starch compared with other resuscitation solutions was not associated with a decrease in mortality. Moreover, after exclusion of 7 trials performed by an investigator whose research has been retracted because of scientific misconduct, hydroxyethyl starch was associated with a significant increased risk of mortality and acute kidney injury. Clinical use of hydroxyethyl starch for acute volume resuscitation is not warranted due to serious safety concerns.

Trials excluding those published by Boldt et al	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)	Weight, %
Haupt and Rackow,[24] 1982	5	9	12	17	0.79 (0.41-1.52)	1.0
Rackow et al,[50] 1989	5	10	5	10	1.00 (0.42-2.40)	0.6
Nagy et al,[23] 1993	4	21	4	20	0.95 (0.27-3.30)	0.3
Beards et al,[49] 1994	4	13	6	15	0.77 (0.28-2.14)	0.4
Berard et al,[26] 1995	32	146	31	153	1.08 (0.70-1.68)	2.2
Younes et al,[48] 1998	2	12	3	11	0.61 (0.12-3.00)	0.2
Asfar et al,[47] 2000	10	16	12	18	0.94 (0.57-1.55)	1.7
Carli et al,[51] 2000	9	85	4	79	2.09 (0.67-6.52)	0.3
Schortgen et al,[3] 2001	28	65	29	64	0.95 (0.64-1.40)	2.8
Veneman et al,[45] 2004	18	30	13	31	1.43 (0.86-2.38)	1.7
Molnar et al,[46] 2004	12	15	10	15	1.20 (0.77-1.86)	2.2
Li et al,[43] 2008	14	30	20	30	0.70 (0.44-1.11)	2.0
McIntyre et al,[22] 2008	9	21	6	19	1.36 (0.59-3.10)	0.6
Brunkhorst et al,[44] 2008	107	297	93	303	1.17 (0.94-1.47)	8.3
Heijden et al,[42] 2009	4	12	8	36	1.50 (0.55-4.11)	0.4
Dolecek et al,[41] 2009	6	26	4	30	1.73 (0.55-5.47)	0.3
Gondos et al,[38] 2010	15	50	38	150	1.18 (0.71-1.96)	1.7
Inal et al,[40] 2010	5	15	5	15	1.00 (0.36-2.75)	0.4
Vlachou et al,[37] 2010	2	12	2	17	1.42 (0.23-8.70)	0.1
Heradstveit et al,[39] 2010	2	10	2	9	0.90 (0.16-5.13)	0.1
Dubin et al,[36] 2010	3	12	7	13	0.46 (0.15-1.40)	0.4
Zhao et al,[21] 2011	3	20	5	20	0.60 (0.17-2.18)	0.3
Zhu et al,[28] 2011	3	90	4	45	0.38 (0.09-1.60)	0.2
Du et al,[35] 2011	2	21	2	21	1.00 (0.16-6.45)	0.1
James et al,[4] 2011	12	58	6	57	1.97 (0.79-4.88)	0.5
Myburgh et al,[54] 2012	597	3500	566	3500	1.05 (0.95-1.17)	38.9
Perner et al,[53] 2012	201	400	172	400	1.17 (1.01-1.36)	19.3
Guidet et al,[52] 2012	40	100	32	96	1.20 (0.83-1.74)	3.1
Subtotal (95% CI)		**5096**		**5194**	**1.09 (1.02-1.17)**	**90.3**
Total events	1154		1101			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{27} = 19.16$; ($P = .86$); $I^2 = 0\%$

Test for overall effect: $Z = 2.39$, ($P = .02$)

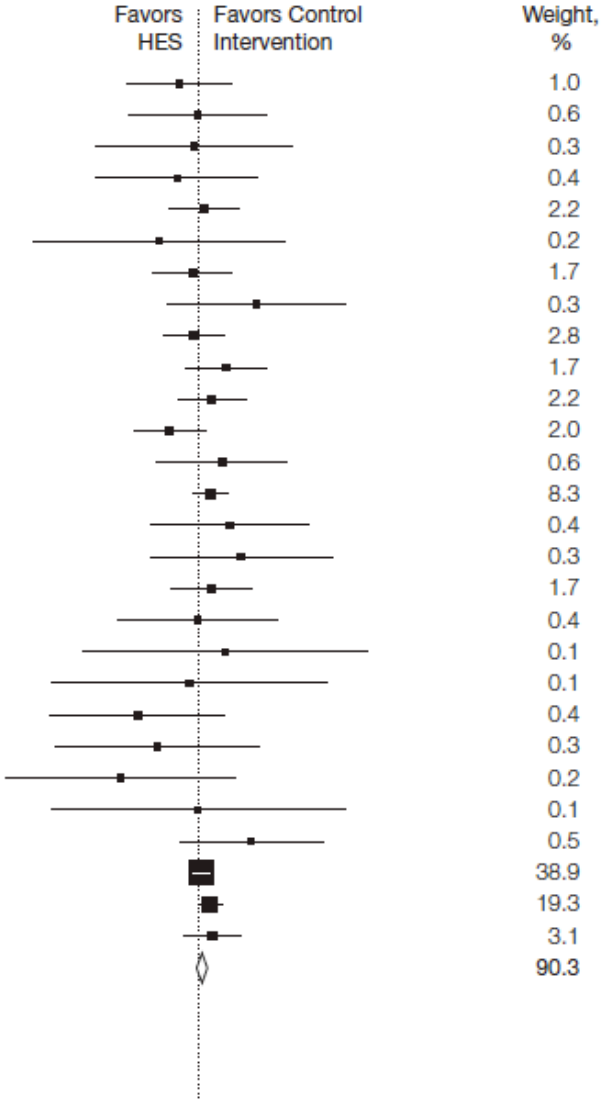
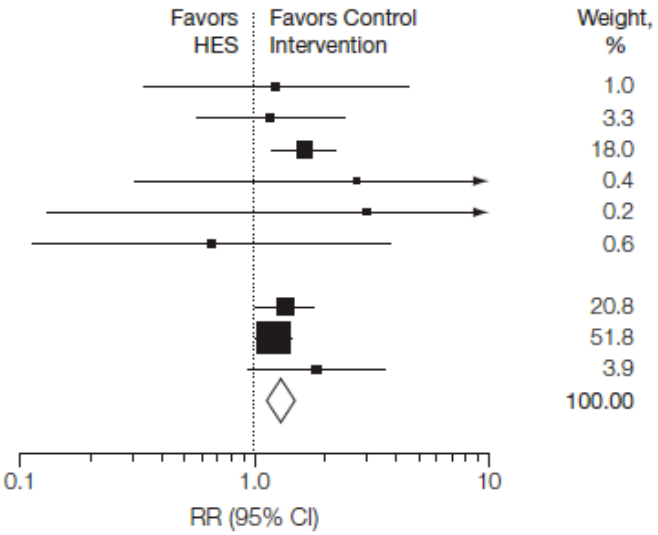


Figure 3. Renal Replacement Therapy and Hydroxyethyl Starch

Source	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)	Weight, %
Berard et al,[26] 1995	5	155	4	152	1.23 (0.34-4.48)	1.0
Schortgen et al,[3] 2001	13	65	11	64	1.16 (0.56-2.40)	3.3
Brunkhorst et al,[44] 2008	81	297	51	303	1.62 (1.19-2.21)	18.0
McIntyre et al,[22] 2008	3	21	1	19	2.71 (0.31-23.93)	0.4
Du et al,[35] 2011	1	21	0	21	3.00 (0.13-69.70)	0.2
James et al,[4] 2011	2	58	3	57	0.66 (0.11-3.78)	0.6
Viachou et al,[37] 2010	0	12	0	17	Not estimable	
Perner al,[53] 2012	87	400	65	400	1.34 (1.00-1.79)	20.8
Myburgh et al,[54] 2012	235	3500	196	3500	1.20 (1.00-1.44)	51.8
Guidet et al,[52] 2012	21	100	11	96	1.83 (0.93-3.59)	3.9
Total (95% CI)		**4629**		**4629**	**1.32 (1.15-1.50)**	**100.00**
Total events	448		342			

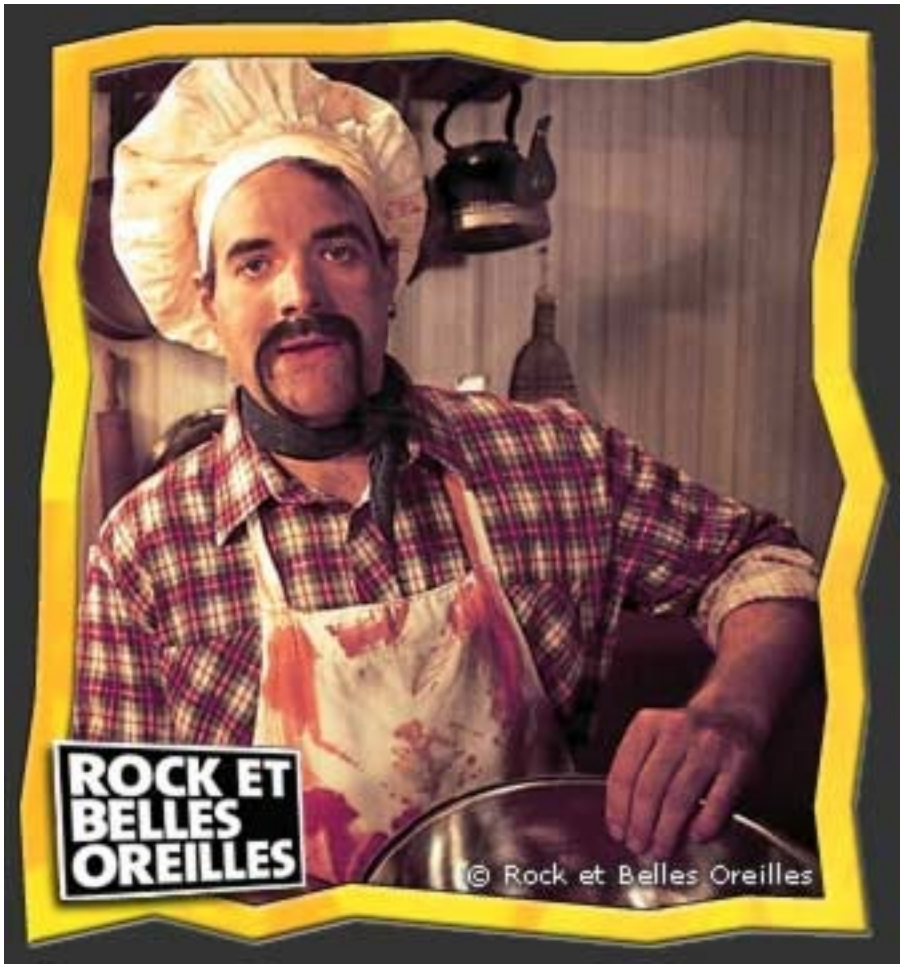
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 5.07$; ($P = .75$); $I^2 = 0\%$

Test for overall effect: $Z = 4.08$, ($P < .001$)



Première méta-analyse

Crastillon

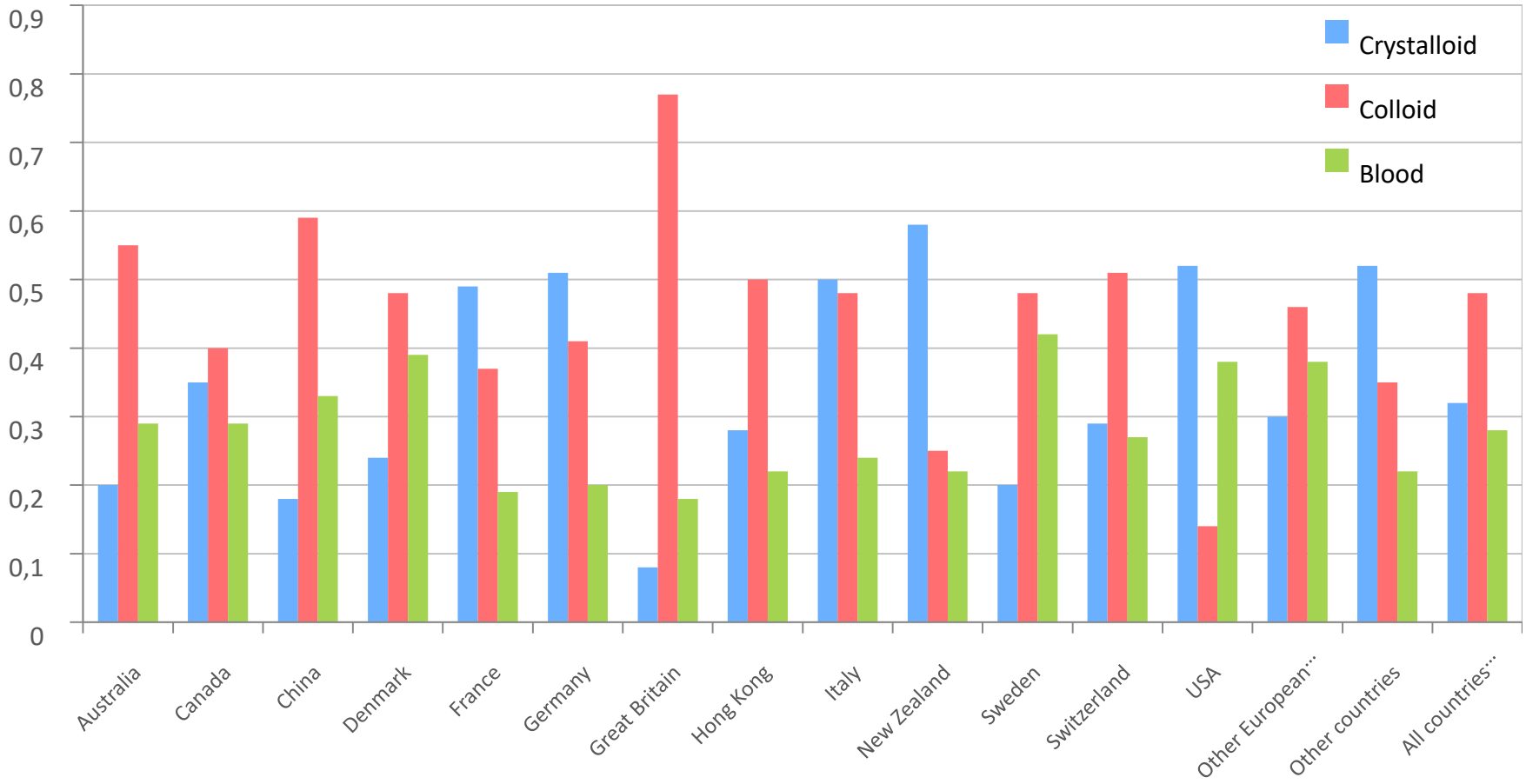


Petite étude poche
+
Petite étude poche
+
Petite étude poche
+
Grosse étude poche
+
Petite étude poche
=
Excellente méta-analyse

http://youtu.be/uX7T3F9En1s

Utilisation solution de remplacement volémique

(SAFE trips 2010)



Chefs d’accusation

1. Coups et blessures
   1. Saignement
   2. Atteinte rénale avec ou sans thérapie de remplacement rénal

2. Homicide involontaire

U.S. Food and Drug Administration

Protecting and Promoting *Your* Health

FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings

Date: November 25, 2013 (Revised)

EUROPEAN MEDICINES AGENCY

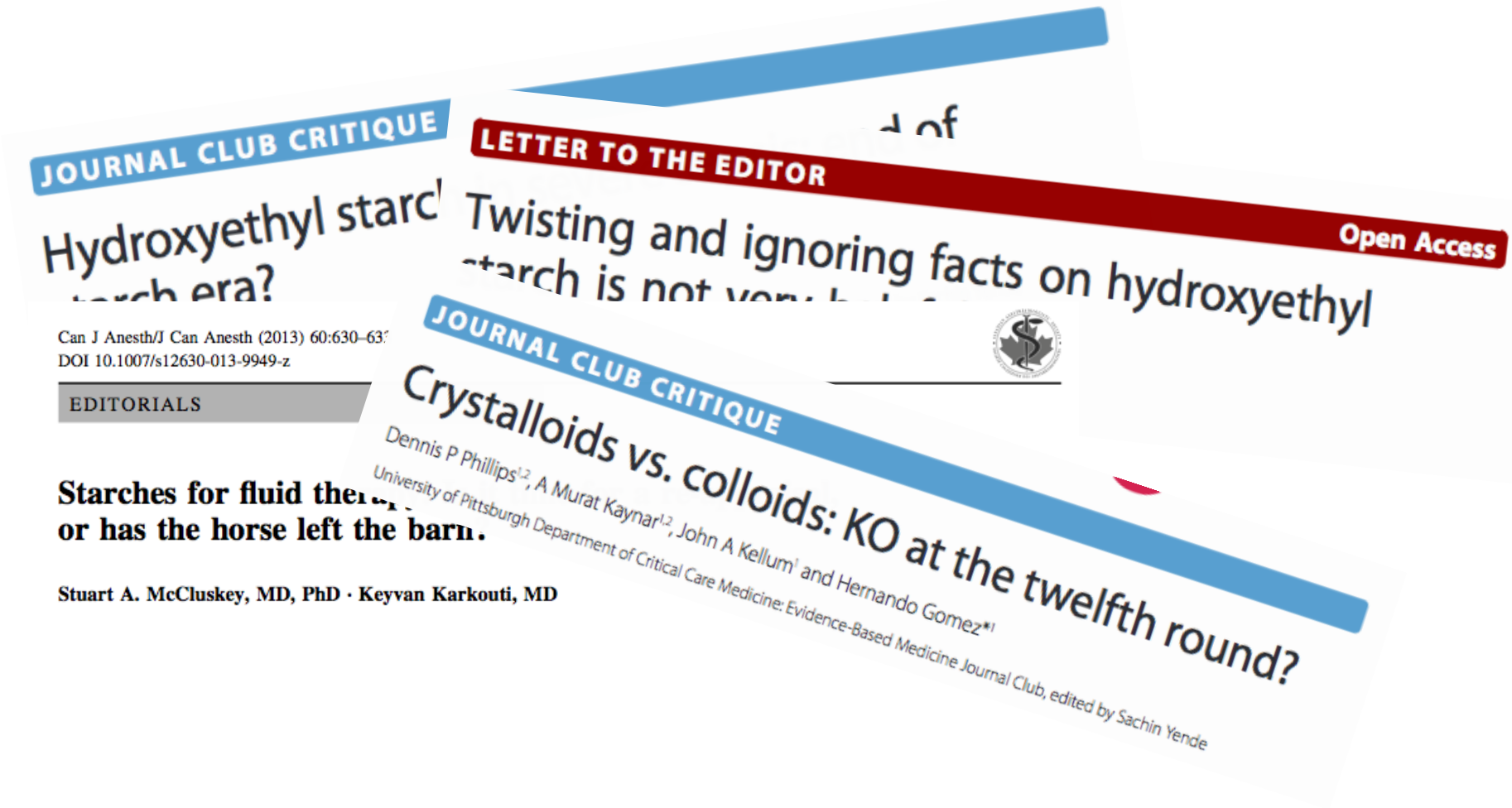
SCIENCE MEDICINES HEALTH

Santé Canada

Défense

1. Ne pas se laisser influencer par l'opinion d'experts
2. Interpréter les évidences
3. Se baser sur les règles de base de l'administration des médicaments

Ne pas se laisser influencer par l'opinion d'expert



Interpréter les évidences

Il y a deux types de clinicien:
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Can Ince, Bruxelles, mars 2013

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

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Des données observationnelles indiquent que **l'utilisation du parachute est associée dans certains cas à la mort et les traumas majeurs** surtout lors de mal fonctionnement et complications iatrogéniques.

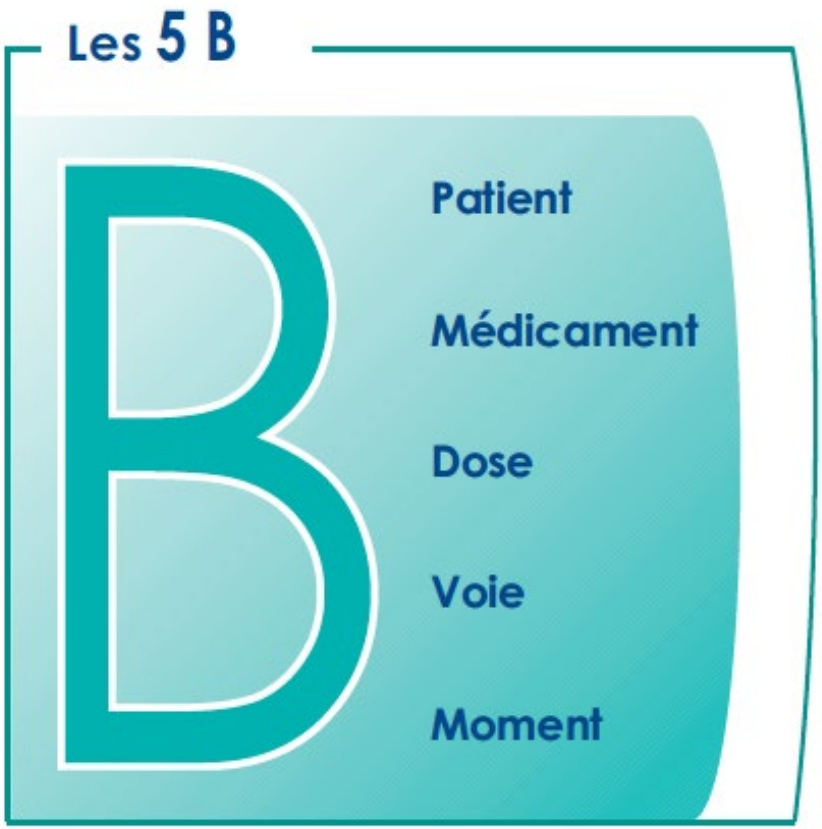
Quelques histoires de cas nous indique **que la chute libre sans parachute n'est pas inévitablement relié à la mort** ou un trauma majeur.

Témoins

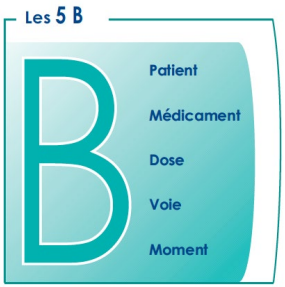
- VISEP
- 6S
- CHEST

- CHRISMAS
- CRYSTAL
- RAFTING
- PRIME

Se baser sur les règles de base de l'administration des médicaments



Le bon Patient



ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

VISEP

SEPSIS SÉVÈRE

Sepsis avec atteinte 1 organe

Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 versus 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

Critical Care 2012, **16**:R94 doi:10.1186/cc11358

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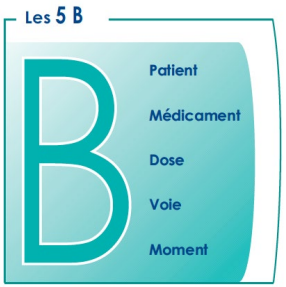
CRYSTMAS

Le bon Patient



ORIGINAL ARTICLE

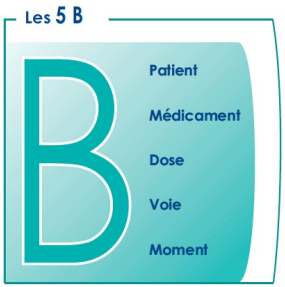
Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

6S

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,

Source of ICU admission — no. (%)		
Emergency department	109 (27)	94 (24)
General ward	177 (44)	196 (49)
Operating or recovery room	59 (15)	54 (14)
Other ICU in the same hospital	21 (5)	14 (4)
Other hospital	32 (8)	42 (10)
Source of sepsis — no. (%)§		
Lungs	212 (53)	229 (57)
Abdomen	130 (33)	133 (33)
Urinary tract	56 (14)	50 (12)
Soft tissue	38 (10)	46 (12)
Other	43 (11)	33 (8)
SAPS II — median (interquartile range)¶	50 (40–60)	51 (39–62)
SOFA score — median (interquartile range)‖	7 (5–9)	7 (5–9)
Shock — no. (%)**	336 (84)	337 (84)
Acute kidney injury — no. (%)††	142 (36)	140 (35)
Mechanical ventilation — no. (%)	240 (60)	245 (61)

Le bon Patient



ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

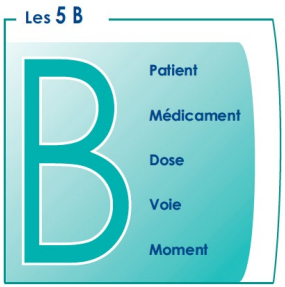
CHEST

CRITÈRES D'INCLUSION

- Patients admis aux soins intensifs
- Jugement clinique de besoin de réplétion volémique

4. The requirement for fluid resuscitation must be supported by AT LEAST ONE of the following clinical signs:
   a. Heart rate >90 beats per minute
   b. Systolic blood pressure < 100 mmHg or mean arterial pressure <75 mmHg or at least 40 mmHg decrease in systolic or mean arterial pressure from the baseline recording
   c. Central venous pressure <10 mmHg
   d. Pulmonary artery wedge pressure <12 mmHg
   e. Respiratory variation in systolic or mean arterial pressure of >5 mmHg
   f. Capillary refill time >1 second
   g. Urine output <0.5 ml/kg for 1 hour

Le bon Patient



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CHEST

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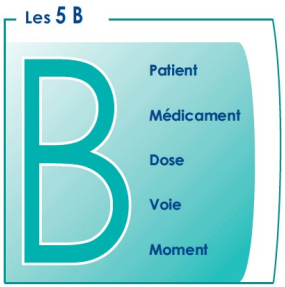
Source of admission to ICU — no./total no. (%)		
Emergency department	930/3353 (27.7)	931/3379 (27.6)
Hospital floor	659/3353 (19.7)	668/3379 (19.8)
Another ICU	53/3353 (1.6)	41/3379 (1.2)
Another hospital	315/3353 (9.4)	306/3379 (9.1)
Operating room		
After emergency surgery	625/3353 (18.6)	630/3379 (18.6)
After elective surgery	771/3353 (23.0)	803/3379 (23.8)
Diagnosis on admission — no./total no. (%)		
Surgical cases	1426/3353 (42.5)	1450/3379 (42.9)
Nonsurgical cases	1920/3353 (57.3)	1926/3379 (57.0)
APACHE II score — median (interquartile range)†	17.0 (12.0–22.0)	17.0 (12.0–23.0)

Le bon Patient



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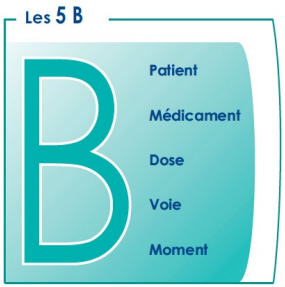
CHEST

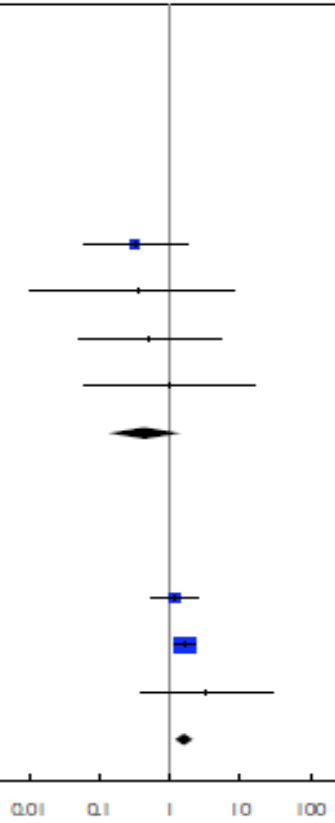
Mechanical ventilation — no./total no. (%)	2131/3326 (64.1)	2177/3354 (64.9)
Use of vasopressor — no./total no. (%)	1520/3337 (45.5)	1551/3361 (46.1)
Serum creatinine — μmol/liter	101.5±57.1	100.1±58.0
Urine output 6 hr before randomization — ml	453.5±418.3	426.6±422.9
Predefined subgroups — no./total no. (%)		
RIFLE criteria for acute kidney injury‡	522/1449 (36.0)	511/1421 (36.0)
Sepsis	979/3355 (29.2)	958/3376 (28.4)
Trauma	267/3358 (8.0)	265/3384 (7.8)
Traumatic brain injury	28/3338 (0.8)	30/3365 (0.9)
APACHE II score ≥25	597/3335 (17.9)	624/3356 (18.6)
Receipt of HES before randomization	509/3347 (15.2)	508/3372 (15.1)

Le bon PATIENT

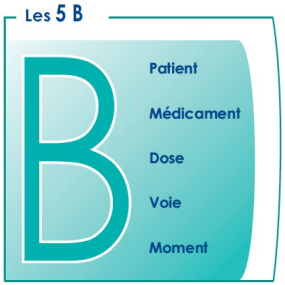


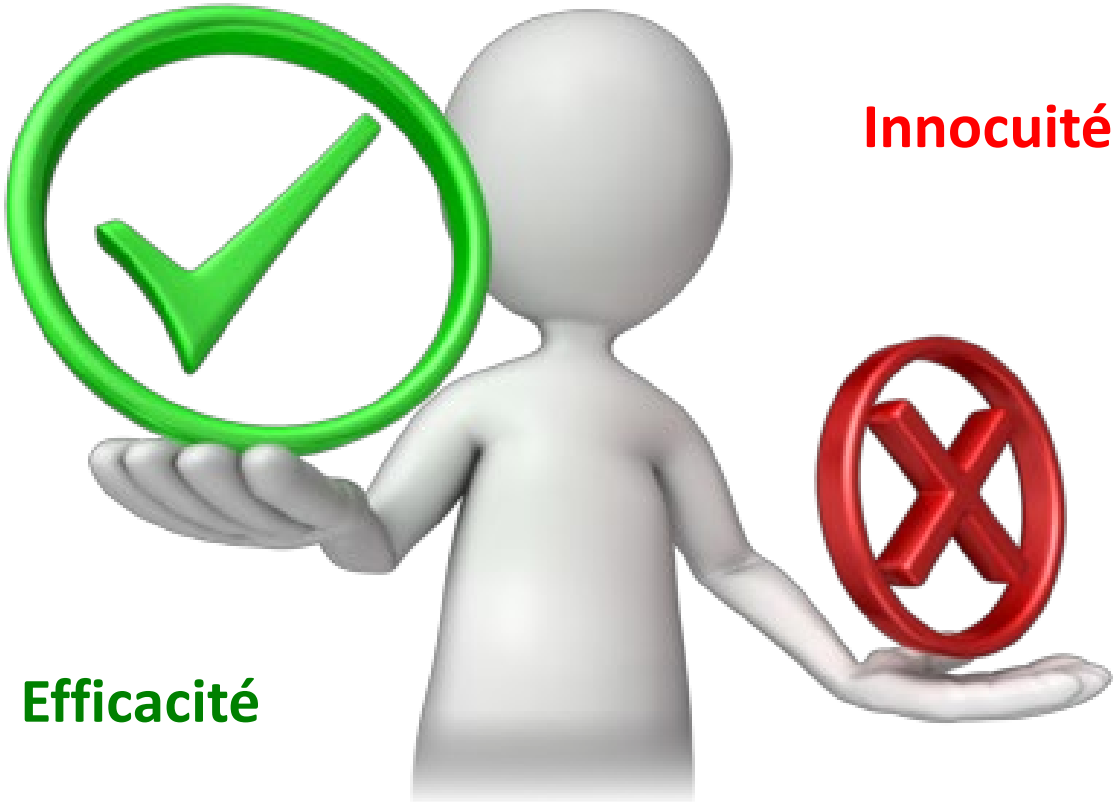
Outcome: 1 Renal replacement therapy

Study or subgroup	HES n/N	Other fluid n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Non-sepsis				
Kumle 1999	0/40	0/20		0.0 [0.0, 0.0]
Boldt 2007a	0/25	0/25		0.0 [0.0, 0.0]
Boldt 2003	0/20	0/20		0.0 [0.0, 0.0]
Boldt 2006	0/25	0/25		0.0 [0.0, 0.0]
Mahmood 2007	2/42	3/20		0.32 [0.06, 1.75]
Godet 2008	0/32	1/33		0.34 [0.01, 8.13]
Boldt 2008	1/30	2/30		0.50 [0.05, 5.22]
London 1989	1/50	1/50		1.00 [0.06, 15.55]
Subtotal (95% CI)	**264**	**223**		**0.44 [0.14, 1.38]**
Total events: 4 (HES), 7 (Other fluid)				
Heterogeneity: Tau² = 0.0; Chi² = 0.52, df = 3 (P = 0.91); I² =0.0%				
Test for overall effect: Z = 1.41 (P = 0.16)				
2 Sepsis				
Schortgen 2001	13/65	11/64		1.16 [0.56, 2.40]
Brunkhorst 2008	81/261	51/272		1.66 [1.22, 2.25]
McIntyre 2008	3/19	1/21		3.32 [0.38, 29.23]
Subtotal (95% CI)	**345**	**357**		**1.59 [1.20, 2.10]**



Le bon MÉDICAMENT





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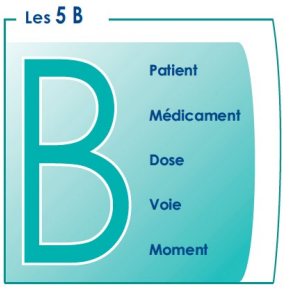
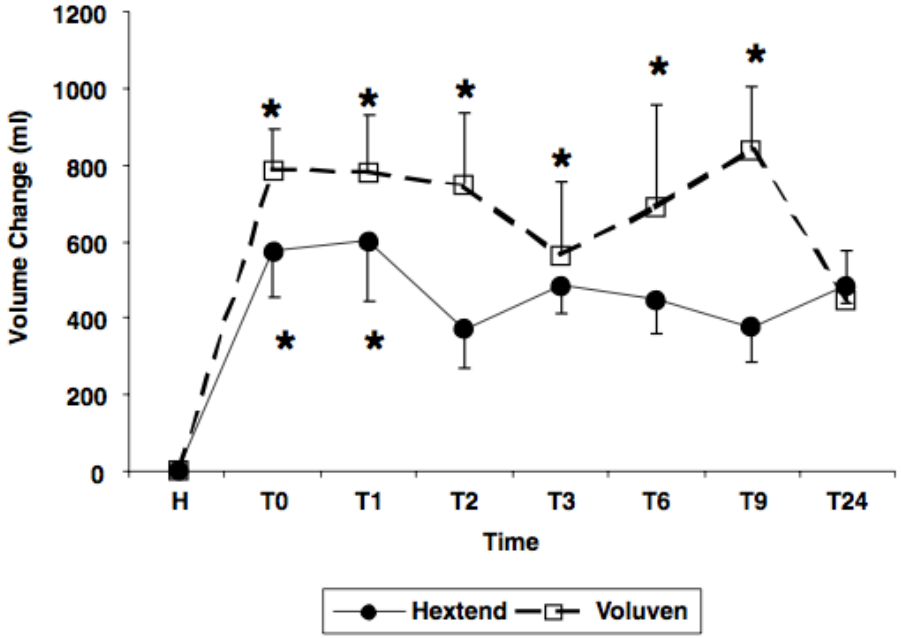


Anaesthesia, 2004, **59**, pages 738–742

Plasma volume changes associated with two hydroxyethyl starch colloids following acute hypovolaemia in volunteers

M. F. M. James,[1,2] M. Y. Latoo,[1] Michael G. Mythen,[1] M. Mutch,[1]
Christian Michaelis,[1] A. M. Roche[1] and Edward Burdett[1]



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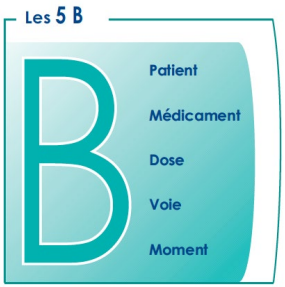

Anesthesiology
1999; 91:1571–6
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Effects of Crystalloid and Colloid Preload on Blood Volume in the Parturient Undergoing Spinal Anesthesia for Elective Cesarean Section

Hiroshi Ueyama, M.D., Yan-Ling He, Ph.D.,† Hironobu Tanigami, M.D.,* Takashi Mashimo, M.D.,‡ Ikuto Yoshiya, M.D.§*

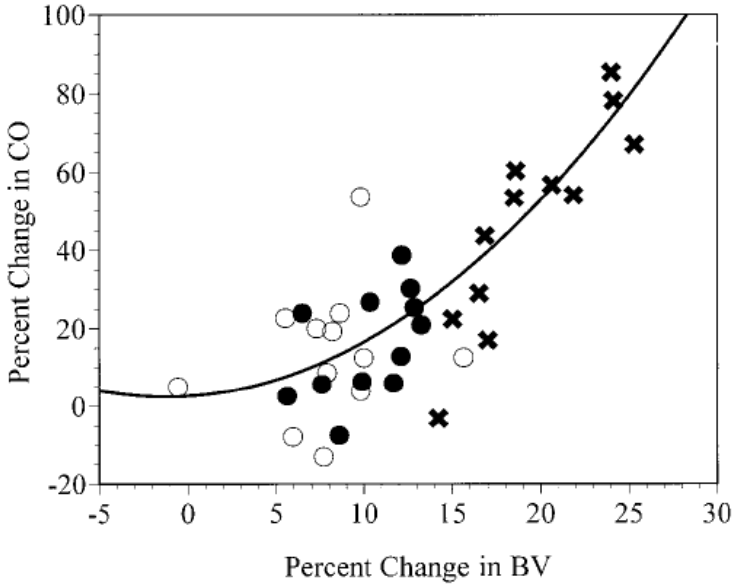
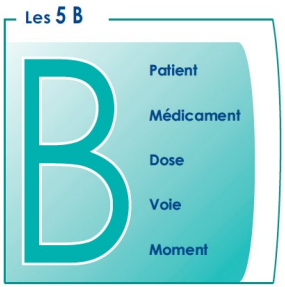


Fig. 1. The relation between percent change in blood volume and cardiac output after volume preload with 1.5 l lactated Ringer's solution (○), 0.5 l hydroxyethylstarch solution, 6% (●), and 1.0 l hydroxyethylstarch solution, 6% (×).

Le bon MÉDICAMENT



Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 versus 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

Critical Care 2012, **16**:R94 doi:10.1186/cc11358

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CRITICAL CARE

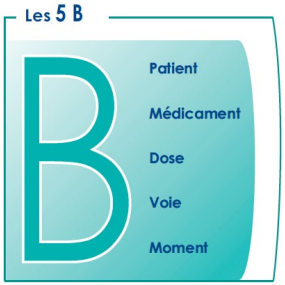
CRYSTMAS

Table 3 Efficacy outcomes.

	HES 130/0.4 (n = 88)	NaCl 0.9% (n = 86)	p
Mean volume of study drug used, ml (SD)	1,379 (886)	1,709 (1,164)	0.0185
Mean time to initial HDS, hours (SD)	11.8 (10.1)	14.3 (11.1)	NS
Number of patients prescribed intravenous catecholamines (%)	88 (88.0)	87 (90.6)	NS

HDS, hemodynamic stabilization; SD, standard deviation; HES, hydroxyethyl starch; NaCl, sodium chloride; NS, not significant.

Le bon MÉDICAMENT

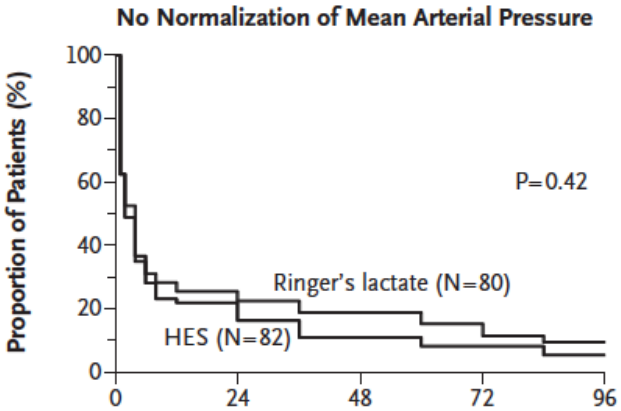


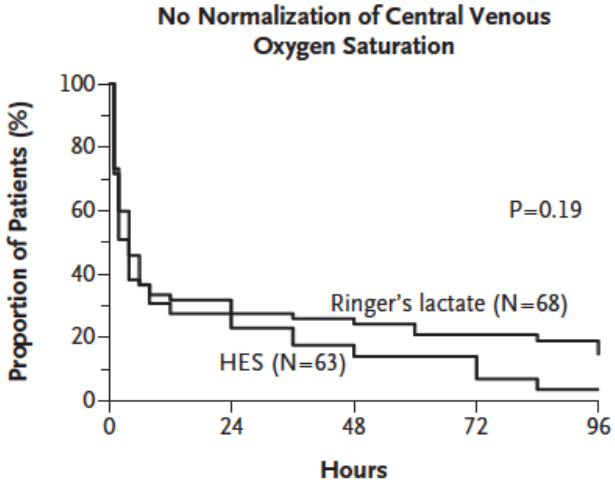
VISEP

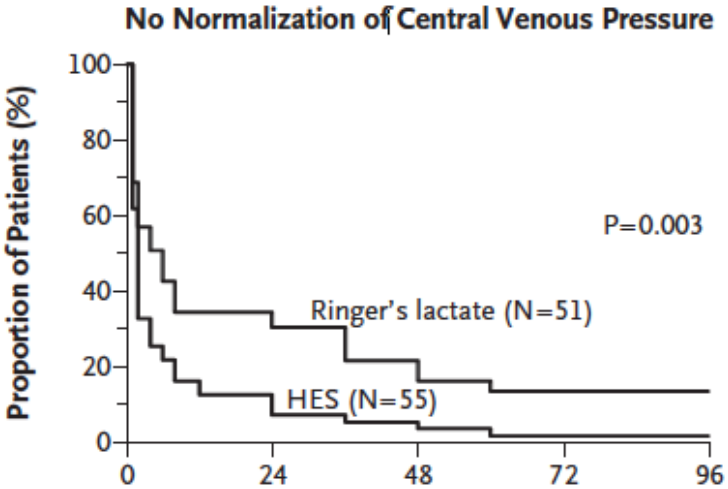
ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)







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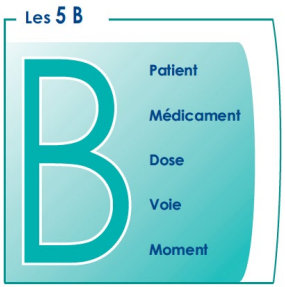

British Journal of Anaesthesia **110** (2): 231–40 (2013)
Advance Access publication 30 October 2012 · doi:10.1093/bja/aes377

BJA

Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm

A. Feldheiser[1], V. Pavlova[1], T. Bonomo[3], A. Jones[1], C. Fotopoulou[2], J. Sehouli[2], K.-D. Wernecke[4] and C. Spies[1*]

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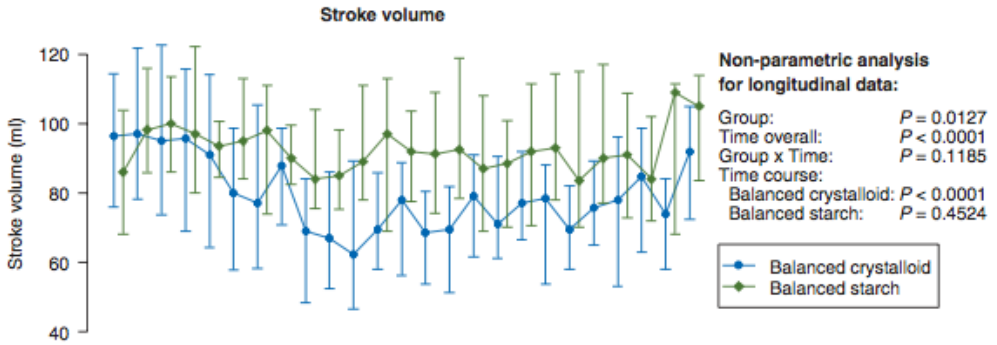

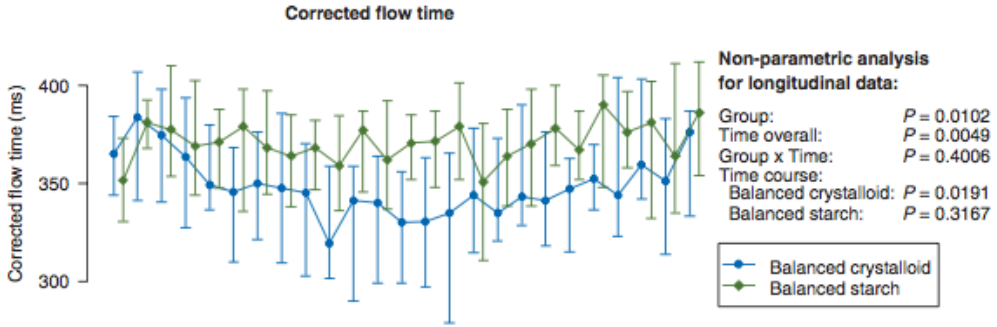

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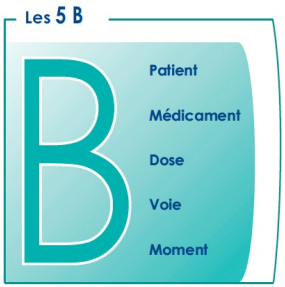


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 1, 2005 VOL. 353 NO. 9

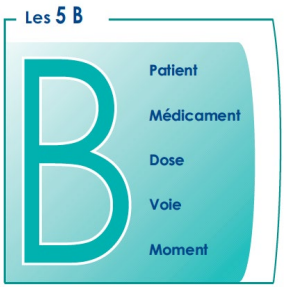
Comparison of Three Fluid Solutions for Resuscitation in Dengue Shock Syndrome

Bridget A. Wills, M.R.C.P., Nguyen M. Dung, M.D., Ha T. Loan, M.D., Dong T.H. Tam, M.D., Tran T.N. Thuy, M.D., Le T.T. Minh, M.D., Tran V. Diet, M.D., Nguyen T. Hao, M.D., Nguyen V. Chau, M.D., Kasia Stepniewska, Ph.D., Nicholas J. White, F.R.C.P., and Jeremy J. Farrar, F.R.C.P.

Table 2. Primary and Secondary Outcome Measures.*

Outcome	Dextran	Starch	Ringer's Lactate	P Value†
Total fluid volume — ml/kg				
Group 1				0.76
Median	100	100	100	
90% range	66–142	70–163	65–157	
Percentage reduction in hematocrit at 2 hr‡				
Group 1				<0.001
Median	25	22	9	
90% range	10–35	7–31	1–19	

Le bon MÉDICAMENT



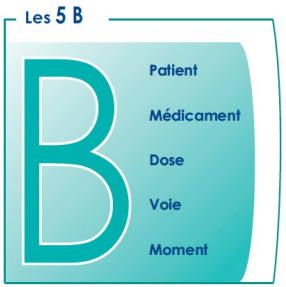
PRIME

Effets d'une dose croissante de colloïde dans l'amorce de CEC

	HES *(24 patients)*	BAL *(25 patients)*	CRYST *(27 patients)*	p
Serum lactate (mmol/L)	**1,05**	**1,28**	**1,48**	HES vs. CRYST:0.003 HES vs. BAL:0,011 BAL vs. CRYST: 0,1621
Additionnal crystalloid CPB (ml)	**189,6**	**456,0**	**925,9**	HES vs. CRYST <0,0001 HES vs. BAL:0,0385 BAL vs. CRYST:0,0032
Additionnal HES CPB (ml)	**12,5**	**82,0**	**194,4**	HES vs. CRYST:0,0017 HES vs. BAL:0,0917 BAL vs. CRYST:0,0789
Fluid balance CPB (ml)	**1270,2**	**1525,8**	**2182,5**	HES vs. CRYST <0,0001 HES vs. BAL:0,0385 BAL vs. CRYST:0,0162
Decrease in Hb (%)	**27,7**	**26,9**	**22,1**	0,0695

Belda 201?

Le bon Médicament



ORIGINAL ARTICLE

6S

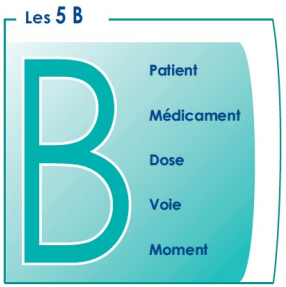
Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,

Table 3. Primary and Secondary Outcomes.*

Outcome	HES 130/0.4 (N=398)	Ringer's Acetate (N=400)	Relative Risk (95% CI)	P Value
Primary outcome				
Dead or dependent on dialysis at day 90 — no. (%)	202 (51)	173 (43)	1.17 (1.01–1.36)	0.03
Dead at day 90 — no. (%)	201 (51)	172 (43)	1.17 (1.01–1.36)	0.03
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
Secondary outcome measures				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic reaction — no. (%)†	1 (0.25)	0	—	0.32
SOFA score at day 5 — median (interquartile range)	6 (2–11)	6 (0–10)	—	0.64
Use of renal-replacement therapy — no. (%)‡	87 (22)	65 (16)	1.35 (1.01–1.80)	0.04
Use of renal-replacement therapy or renal SOFA score ≥3 — no. (%)§	129 (32)	108 (27)	1.20 (0.97–1.48)	0.10
Doubling of plasma creatinine level — no. (%)†	148 (41)	127 (35)	1.18 (0.98–1.43)	0.08
Acidosis — no. (%)†¶	307 (77)	312 (78)	0.99 (0.92–1.06)	0.72
Alive without renal-replacement therapy — mean % of days‖	91	93	—	0.048
Use of mechanical ventilation — no. (%)†	325 (82)	321 (80)	1.02 (0.95–1.09)	0.61
Alive without mechanical ventilation — mean % of days‖	62	65	—	0.28
Alive and out of hospital — mean % of days‖	29	34	—	0.048

Le bon Médicament



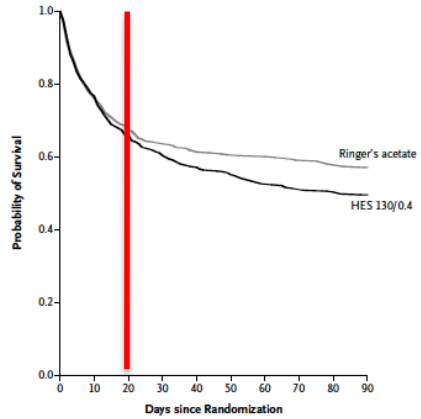
ORIGINAL ARTICLE

6S

Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,

A Time to Death

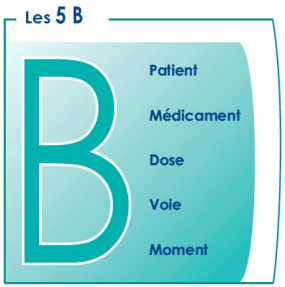


No. at Risk				
HES 130/0.4	398	240	209	197
Ringer's acetate	400	254	240	228

B Relative Risk of the Primary Outcome

Subgroup	HES 130/0.4	Ringer's Acetate	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. in subgroup			
Shock at the time of randomization				0.22
Yes	179/336	148/337	1.21 (1.04–1.42)	
No	23/62	25/63	0.93 (0.60–1.46)	
Acute kidney injury at the time of randomization				0.60
Yes	72/142	63/140	1.13 (0.88–1.44)	
No	130/256	110/260	1.20 (1.00–1.45)	
All patients	202/398	173/400	1.17 (1.01–1.36)	

Le bon Médicament

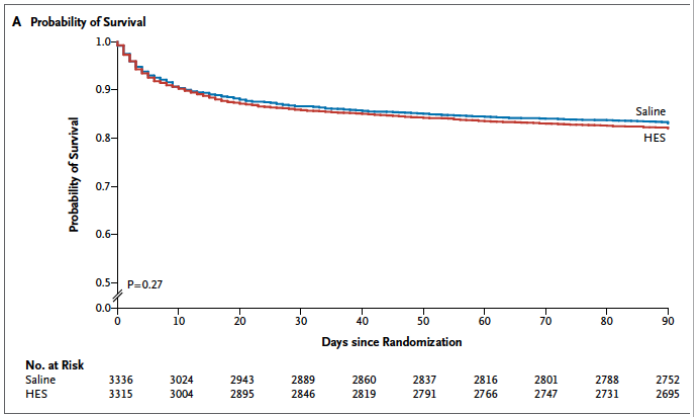


ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

CHEST



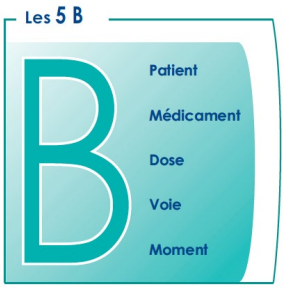
B Subgroup Analyses

Subgroup	HES	Saline	Risk Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Death from any cause at 90 days	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96–1.18)	0.26
RIFLE criteria at randomization				0.66
Presence of acute renal injury	99/519 (19.1)	95/503 (18.9)	1.01 (0.78–1.30)	0.94
Absence of acute renal injury	132/919 (14.4)	118/896 (13.2)	1.09 (0.87–1.37)	0.46
Sepsis at randomization				0.78
Diagnosis on admission	248/976 (25.4)	224/945 (23.7)	1.07 (0.92–1.25)	0.38
No diagnosis on admission	349/2337 (14.9)	342/2383 (14.4)	1.04 (0.91–1.19)	0.57
Trauma				0.90
Yes	18/258 (7.0)	18/263 (6.8)	1.02 (0.54–1.91)	0.95
No	579/3057 (18.9)	548/3073 (17.8)	1.06 (0.96–1.18)	0.26
Traumatic brain injury				0.31
Yes	1/27 (3.7)	3/30 (10.0)	0.37 (0.04–3.35)	0.35
No	594/3269 (18.2)	560/3287 (17.0)	1.07 (0.96–1.18)	0.23
APACHE II score before randomization				0.60
≥25	217/590 (36.8)	221/616 (35.9)	1.03 (0.88–1.19)	0.74
<25	372/2702 (13.8)	342/2690 (12.7)	1.08 (0.94–1.24)	0.25
Receipt of HES before randomization				0.78
Yes	48/508 (9.4)	42/499 (8.4)	1.12 (0.76–1.67)	0.57
No	547/2798 (19.5)	522/2825 (18.5)	1.06 (0.95–1.18)	0.31

0.25 1.00 4.00

HES Better Saline Better

Le bon Médicament



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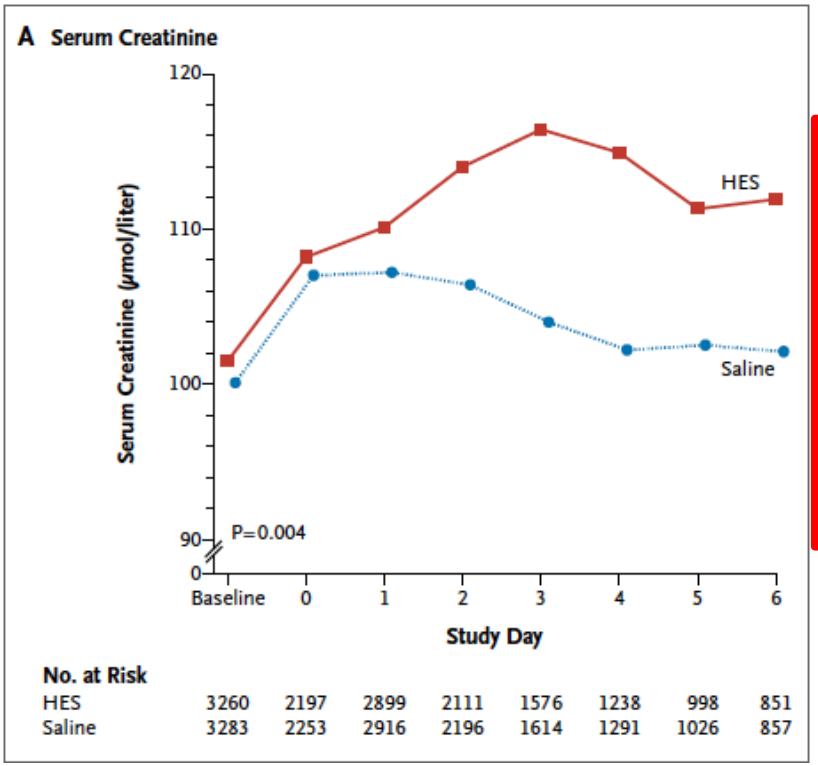

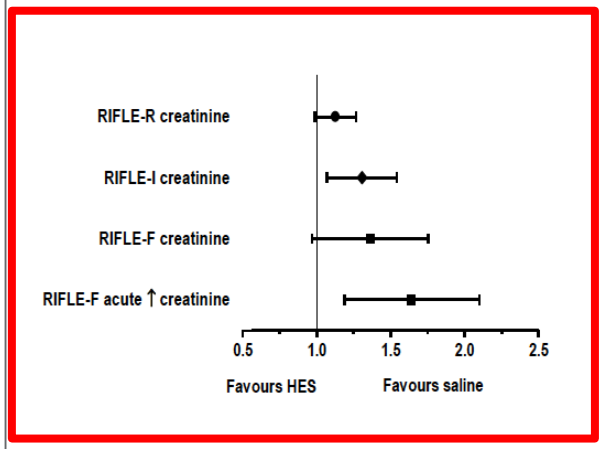

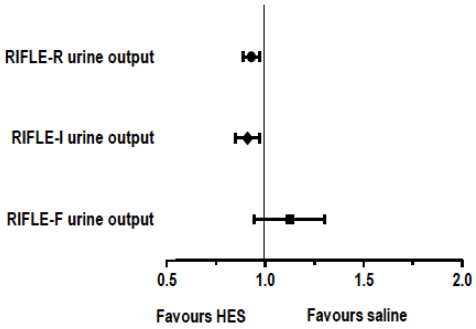

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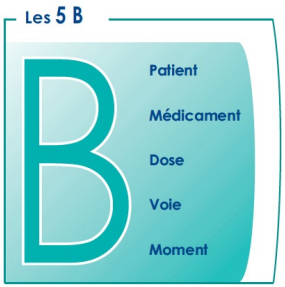


Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

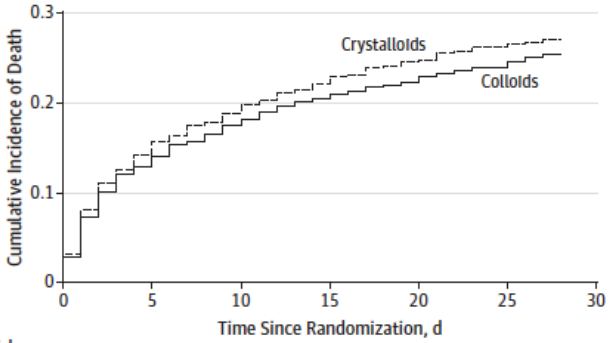
CRYSTAL

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descorps Declère, MD; Jean Charles Preiser, MD; Hervé Outin, MD; Gilles Troché, MD; Claire Charpentier, MD; Jean Louis Trouillet, MD; Antoine Kimmoun, MD; Xavier Forceville, MD, PhD; Michael Darmon, MD; Olivier Lesur, MD, PhD; Jean Régnier, MD; Fékri Abroug, MD; Philippe Berger, MD; Christophe Clech, MD; Joël Cousson, MD; Laure Thibault, MD; Sylvie Chevret, MD, PhD; for the CRISTAL Investigators

Table 3. Mortality Outcomes in Patients Who Received Only 1 Type of Fluid

	Colloids Group, No.		Crystalloids Group, No.		
	Patients	Deaths	Patients	Deaths	HR (95% CI)
28-d Mortality					
Entire population	1414	359	1443	390	0.92 (0.80-1.07)
HES vs isotonic saline	645	149	1035	275	0.83 (0.68-1.01)
Gelatins vs isotonic saline	281	69	1035	275	0.90 (0.69-1.17)
HES vs Ringer solution	645	149	72	22	0.71 (0.45-1.11)
Gelatins vs Ringer solution	281	69	72	22	0.78 (0.48-1.26)
Albumin vs isotonic saline	80	24	1035	275	1.10 (0.72-1.68)
90-d Mortality					
Entire population	1414	434	1443	493	0.88 (0.77-0.99)
HES vs isotonic saline	645	181	1035	346	0.79 (0.66-0.95)
Gelatins vs isotonic saline	281	84	1035	346	0.87 (0.68-1.10)
HES vs Ringer solution	645	181	72	26	0.72 (0.48-1.09)
Gelatins vs Ringer solution	281	84	72	26	0.80 (0.51-1.24)
Albumin vs isotonic saline	80	28	1035	346	1.02 (0.69-1.50)

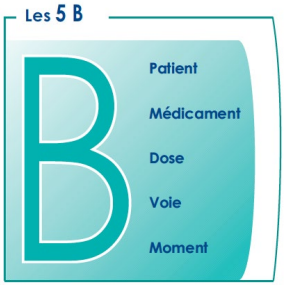
Figure 2. Cumulative Incidence of Death Within First 28 Days After Randomization

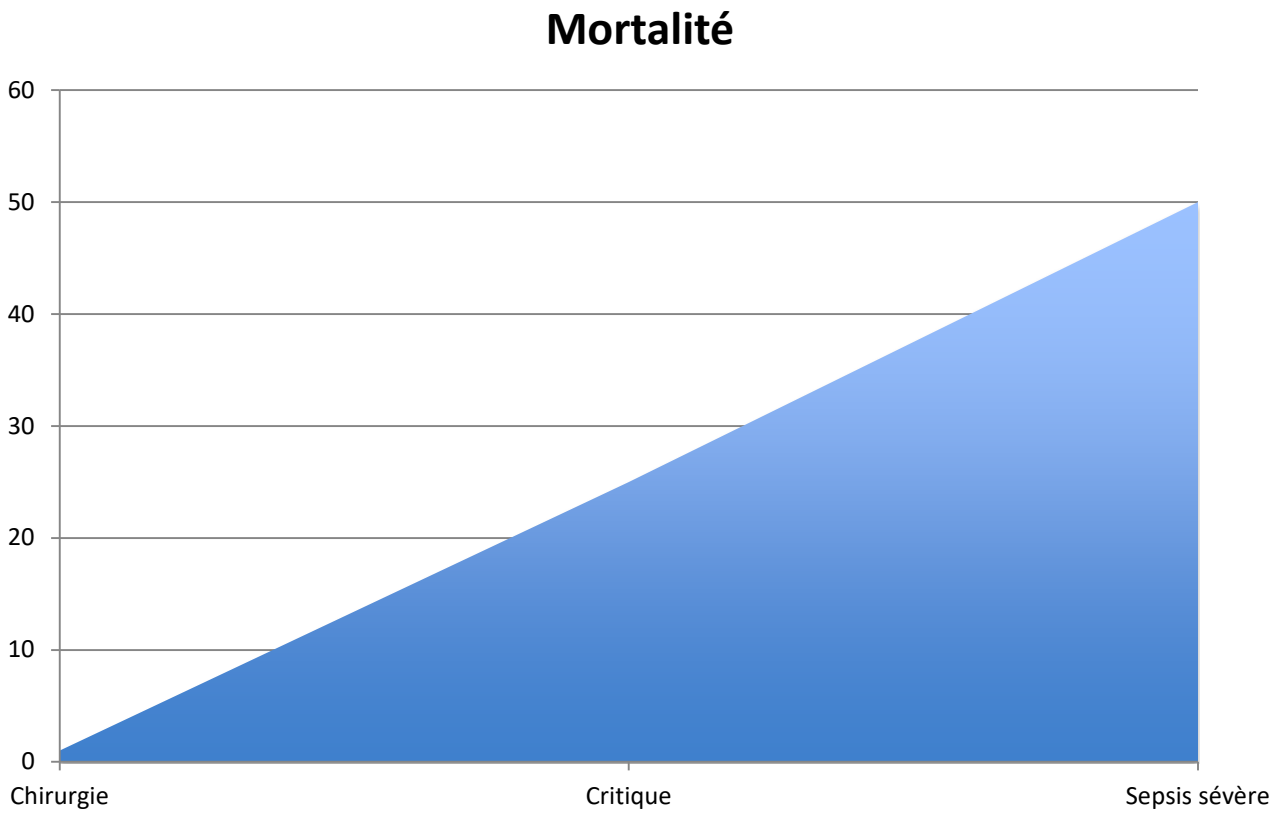


No. at risk

Colloids	1414	1233	1167	1124	1099	1076
Crystalloids	1443	1239	1172	1124	1089	1064

Le bon MÉDICAMENT





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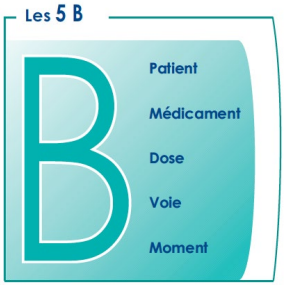
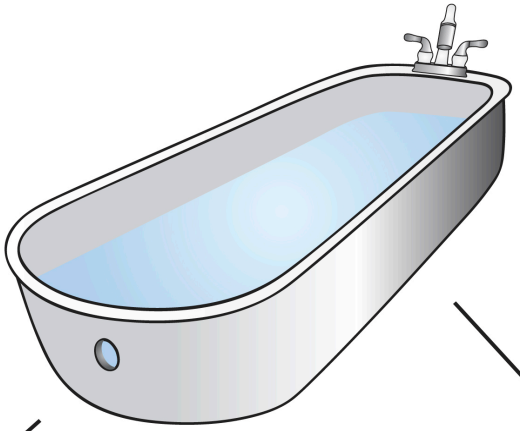
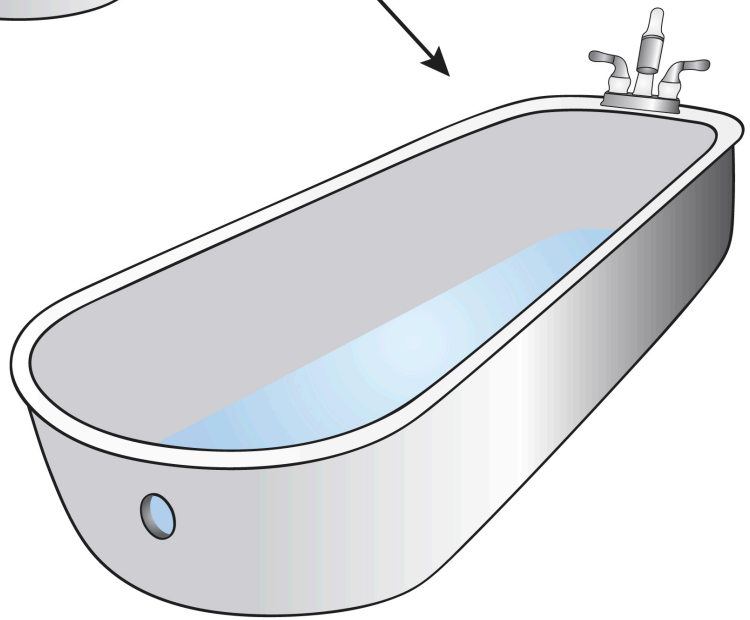




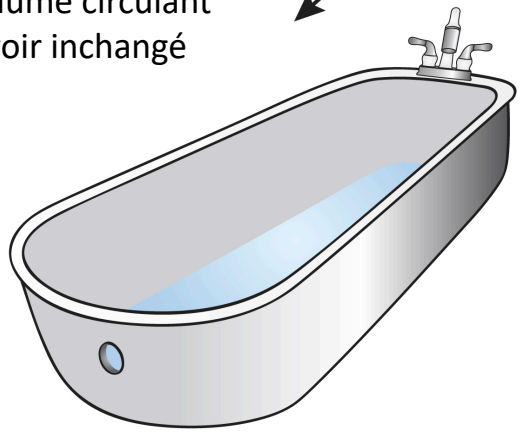
SEPSIS

Volume circulant inchangé
Augmentation volume du réservoir

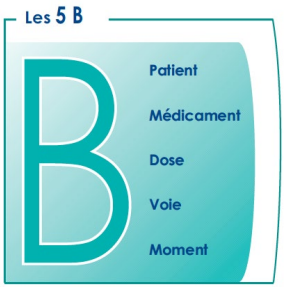


SAIGNEMENT

Diminution du volume circulant
Volume du réservoir inchangé



Le bon MÉDICAMENT



The impact of the glycocalyx on microcirculatory oxygen distribution in critical illness

Daniel Chappell[a], Martin Westphal[b] and Matthias Jacob[a]

[a]Clinic of Anaesthesiology, Ludwig-Maximilians University Munich, Munich and [b]Department of Anaesthesiology and Intensive Care, University of Muenster, Muenster, Germany

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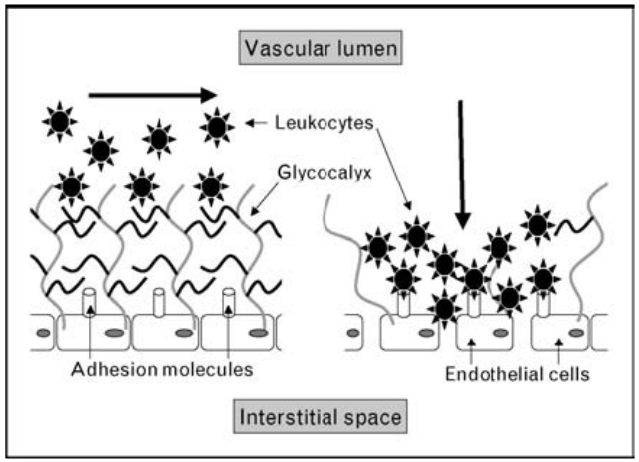
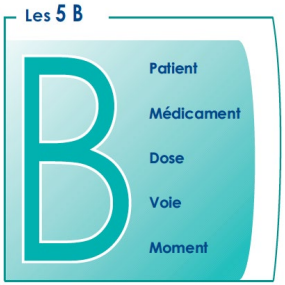
Current Opinion in Anaesthesiology 2009, 22:155–162

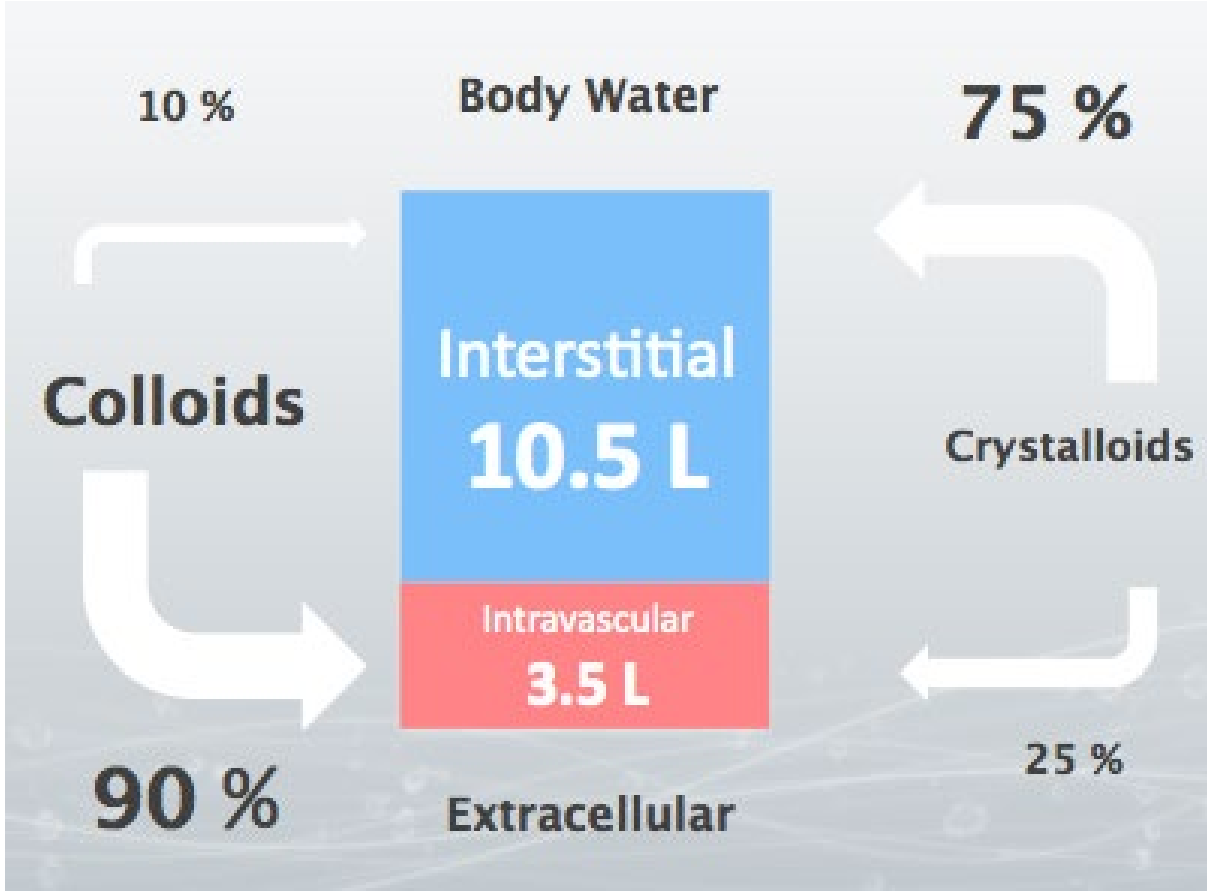
Figure 2 A schematic image of the intact and a degraded glycocalyx



(a) An image of the intact and a degraded glycocalyx. Nonactivated leucocytes flow in the normal blood stream above the glycocalyx and do not come in contact with endothelial adhesion molecules harboured within the glycocalyx. (b) The situation changes when the glycocalyx is degraded. Adhesion molecules are exposed, activated and interact with leucocytes, causing activation, conglomeration, adhesion and migration.

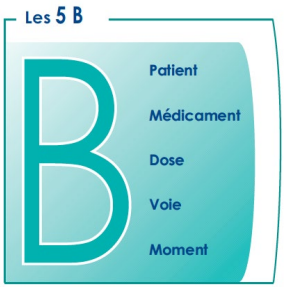
La bonne DOSE





Dans les études cliniques, le ratio crystalloïdes/colloïdes pour atteindre des objectifs prédéterminés de réplétion volémique varie entre **1,6 à 2,1**

La bonne DOSE

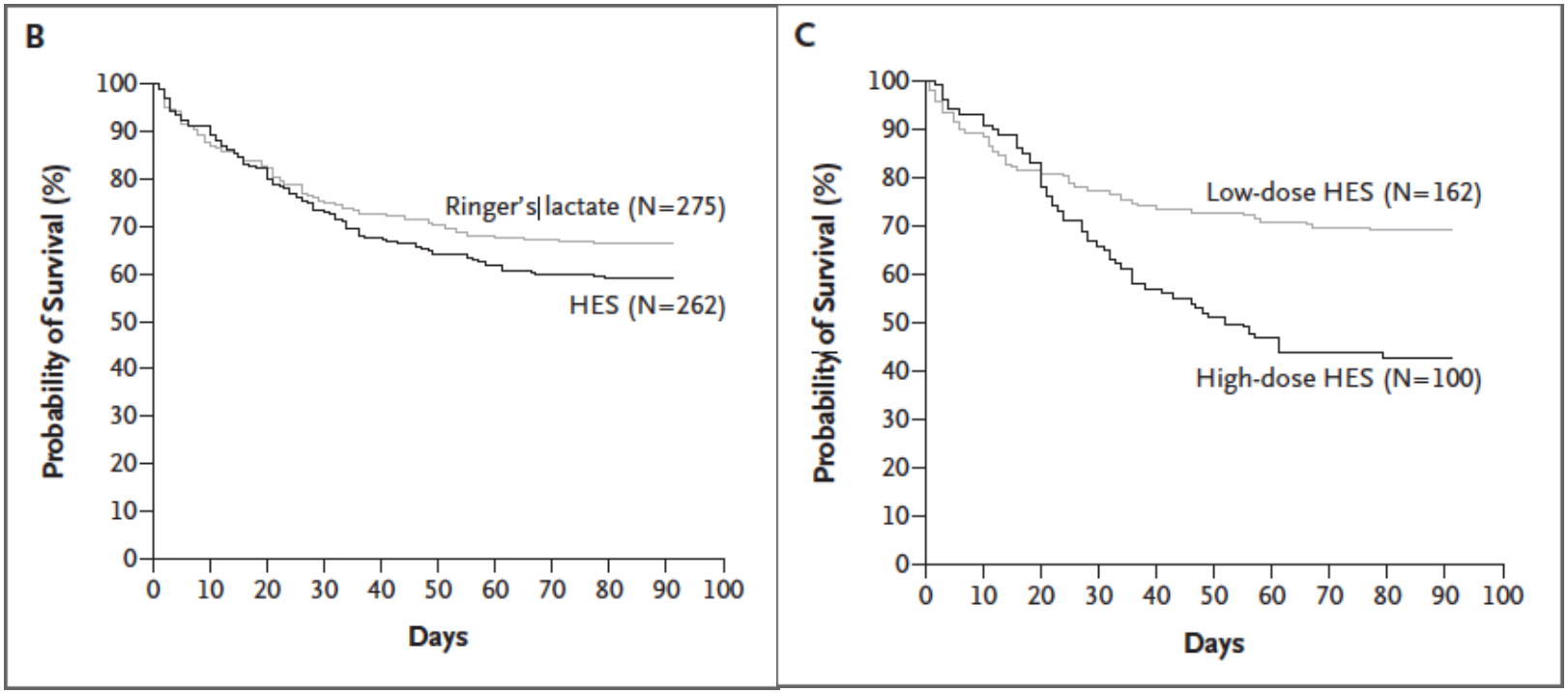


ORIGINAL ARTICLE

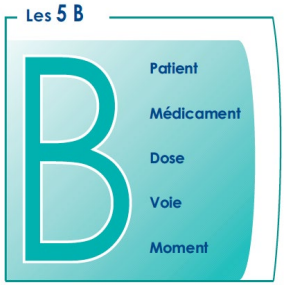
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

VISEP



La bonne DOSE



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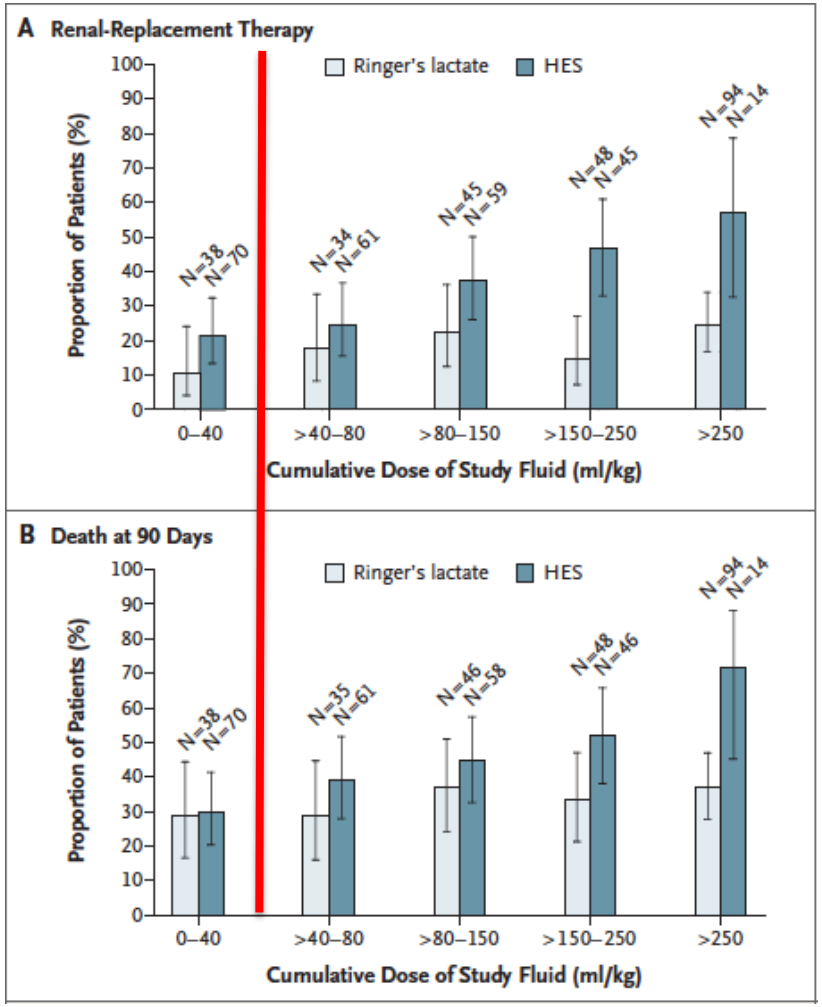
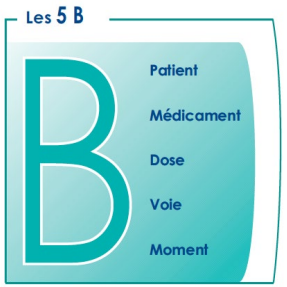
Low dose < 22cc/Kg



La bonne DOSE



ORIGINAL ARTICLE

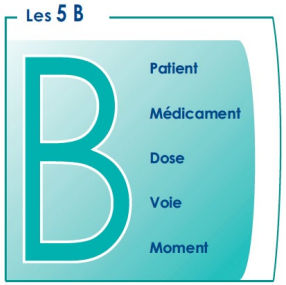
Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D.,

Table 2. Fluid Therapy before and after Randomization.*

Variable	HES 130/0.4 (N=398)			Ringer's Acetate (N=400)			P Value†
	Patients	Volume Received‡		Patients	Volume Received‡		
		median	interquartile range		median	interquartile range	
	no./total no.§	*ml*		*no./total no.§*	*ml*		
Trial fluid							
Day 1¶	374/397	1500	1000–1500	375/400	1500	1000–2000	0.09
Day 2	288/379	1500	1000–2000	307/380	1500	950–2000	0.50
Day 3	176/330	1000	500–1500	170/326	1000	500–1500	0.78
Open-label trial fluid							
Day 1¶	157/397	1500	1000–2000	177/400	1500	800–2500	0.21
Day 2	114/379	1000	500–1500	133/380	1000	500–2000	0.13
Day 3	54/329	900	500–1000	57/326	1000	500–1250	0.69
Other fluids‖							
Day −1**	356/366	3500	2000–4938	370/385	3000	2000–4868	0.08
Day 1¶	389/394	2235	1325–3197	393/396	1976	1077–3046	0.12
Day 2	373/376	2980	2143–3960	369/371	2905	2094–3780	0.50
Day 3	313/316	3150	2365–3910	315/317	3035	2183–3924	0.33
Blood products††							
Day −1**	90/392	838	480–1435	88/399	600	490–1195	0.69
Day 1¶	109/397	590	300–1100	89/400	600	490–980	0.13
Day 2	115/378	600	350–1100	78/379	526	300–1030	0.001
Day 3	81/327	500	300–980	68/326	598	300–750	0.28
Total‡‡	243/376	1340	566–2700	204/380	1055	600–2755	0.003

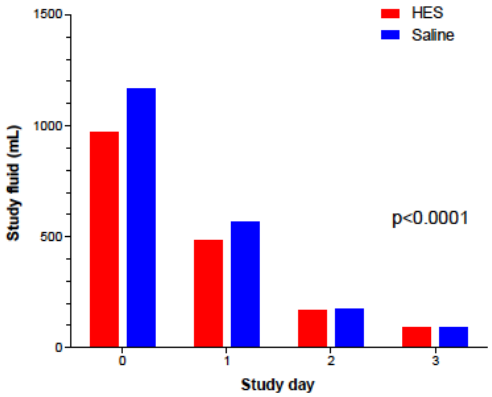
La bonne DOSE

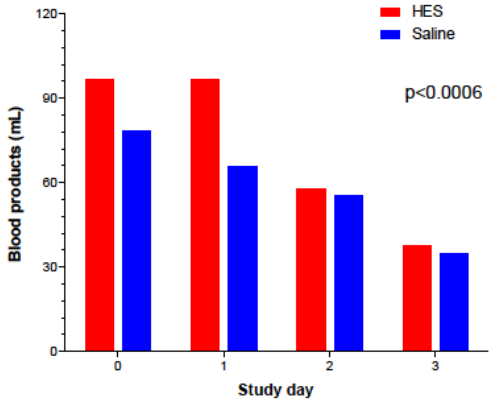


ORIGINAL ARTICLE

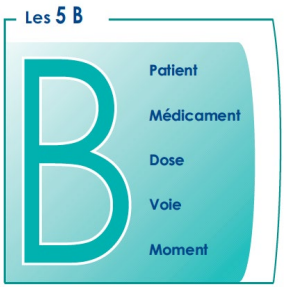
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*





Le bon MOMENT



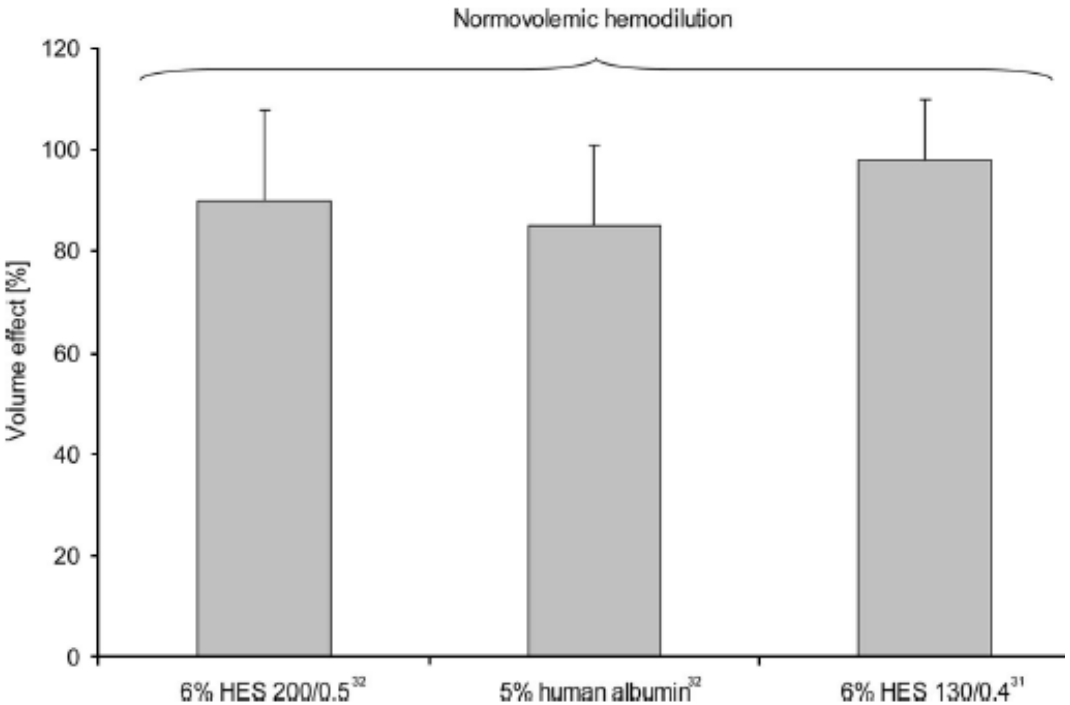
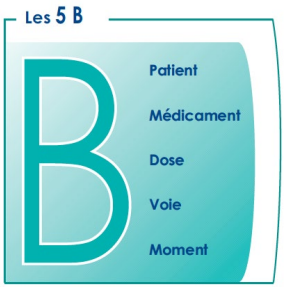
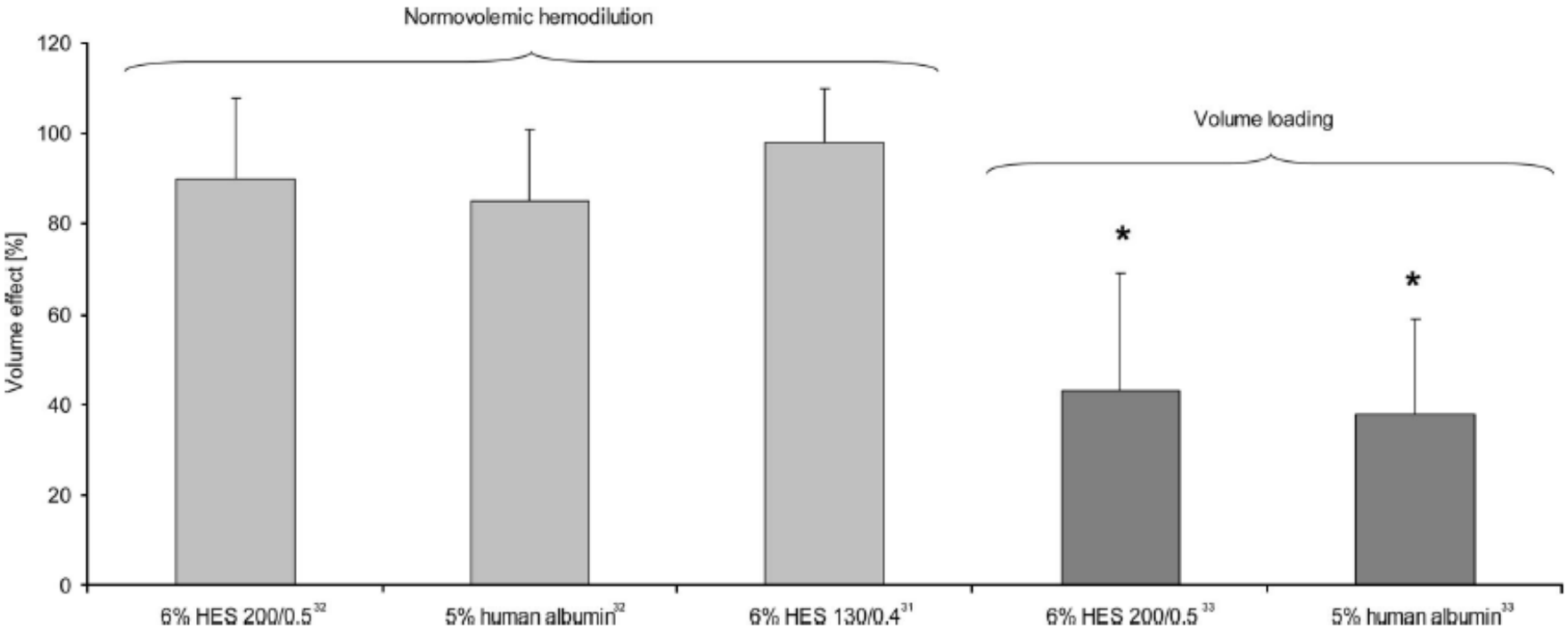


Fig. 5. The context sensitivity of volume effects of iso-oncotic colloids (the volume effect is that part of the colloid that remains within the circulation and does not primarily shift outward). As a substitute during acute bleeding, carefully maintaining normovolemia throughout the procedure, 6% hydroxyethyl starch (HES) 200/0.5, 5% human albumin, and 6% HES 130/0.4 (*left columns*) had volume effects of more than 90%. Volume loading of the normovolemic, by contrast, led to volume effects of 6% HES 200/0:5 and 5% human albumin (*right columns*) of approximately 40%. Blood volumes were assessed before and after intervention *via* double-label technique.[31–33] n = 10 each. Values are mean ± SD. * $P < 0.05$ *versus* normovolemic hemodilution.

Le bon MOMENT





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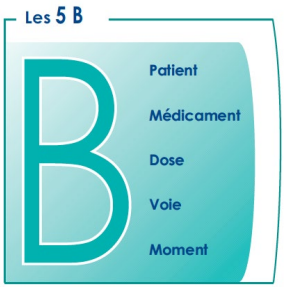
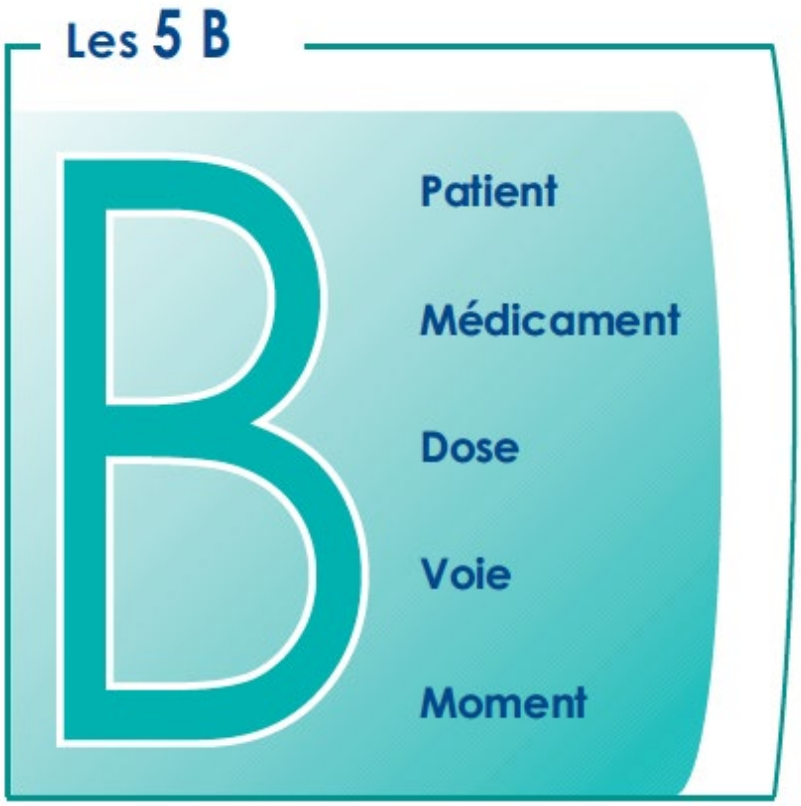


Table 1. Characteristics of the Patients at Baseline.*

Characteristic	HES (N=3358)	Saline (N=3384)
Time from ICU admission to randomization — hr	10.9±156.5	11.4±165.4
Physiological variables		
Heart rate — beats/min	89.3±23.6	88.8±23.3
Mean arterial pressure — mm Hg	74.0±14.9	73.7±14.6
Central venous pressure — mm Hg	9.5±5.4	8.9±5.1
Lactate — mmol/liter	2.1±2.0	2.0±1.5
Mechanical ventilation — no./total no. (%)	2131/3326 (64.1)	2177/3354 (64.9)
Use of vasopressor — no./total no. (%)	1520/3337 (45.5)	1551/3361 (46.1)

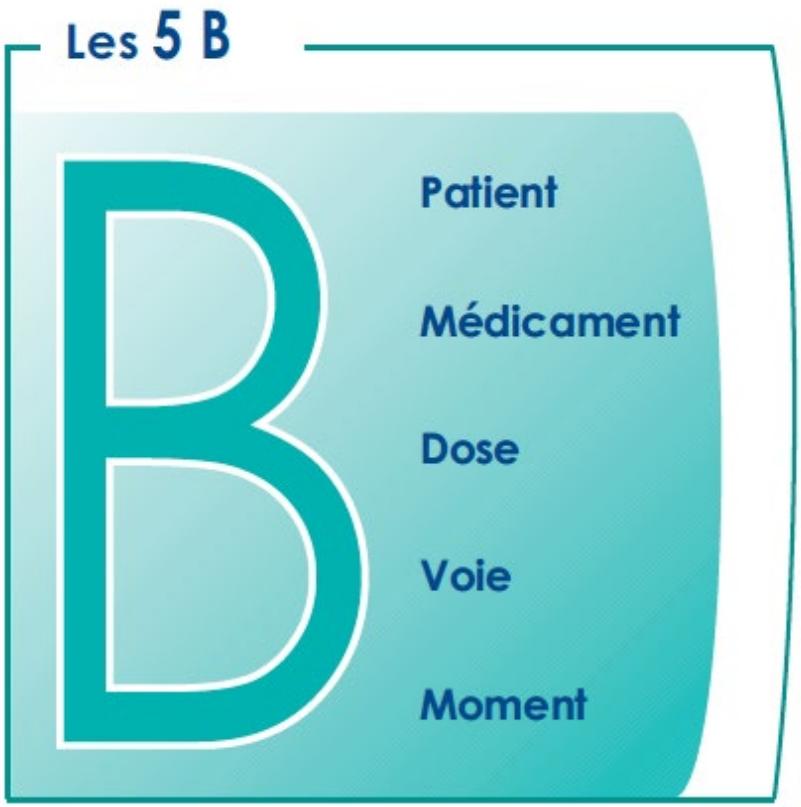
Les évidences

- Les récentes études randomisaient des patients majoritairement septiques.
- Une minorité de patients chirurgicaux et encore moins de chirurgies électives.
- Le besoin de réplétion volémique chez ces patients était souvent mal défini.
- Les patients étaient dans un état critique avec de multiples comorbidités et fréquemment une atteinte rénale.
- Il est impossible d'appliquer directement les conclusions de ces études aux patients en salle d'opération.



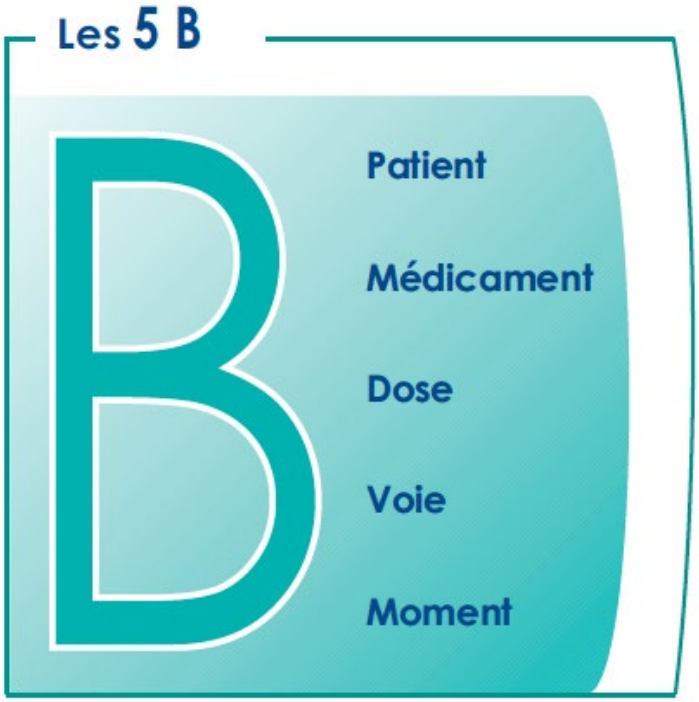
Les évidences

- Le HES 130/0,4 semble avoir une potentiel de réplétion volémique supérieur aux crystalloïdes.
- Il devrait être utilisé pour une réplétion de perte absolue de volume sanguin seulement.
- Son utilisation devrait être fait avec un monitoring des indices de remplissage ou de perfusion.
- La quantité minimale de HES devrait être utilisée pour atteindre les objectifs de réplétion volémique.



Les évidences

- Il ne devrait pas être utilisé dans les cas de sepsis.
- Il ne devrait pas être utilisé chez des patients avec une fonction rénale altérée.
- La fonction rénale devrait être monitorisée chez les patients qui reçoivent du HES 130/0,4.
- La créatinine est un critère de suivi objectif tandis que le besoin de TRR est subjectif
- Le risque accru de TRR pourrait être secondaire à une augmentation de la pression veineuse ou de l'hypervolémie

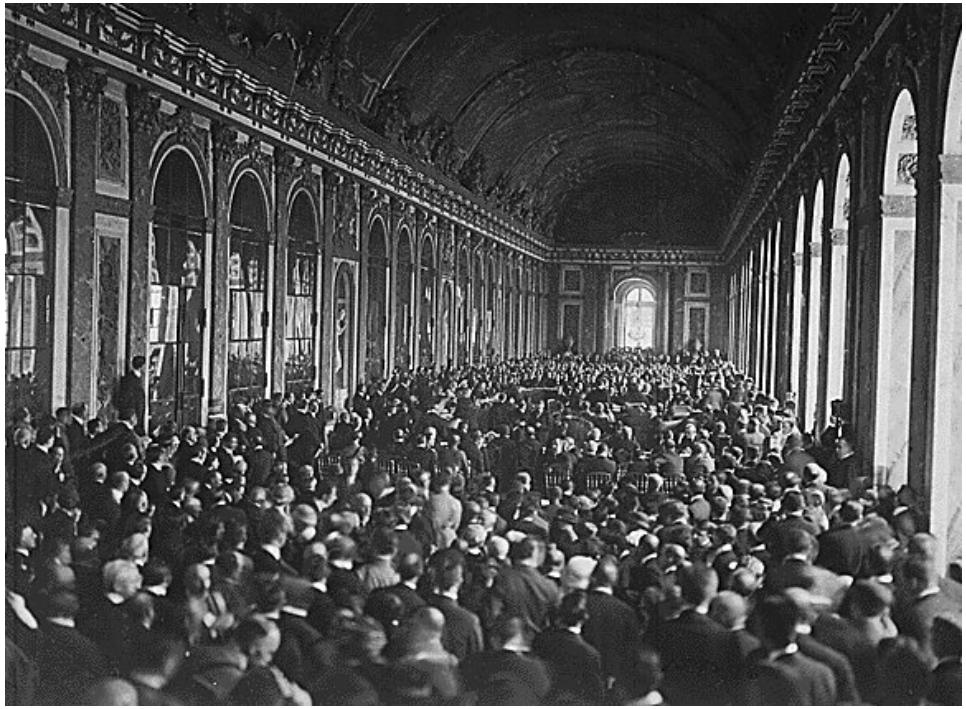


Délibération du jury

Devrait-on encore utiliser du HES 130/0.4 dans le traitement de l'hypovolémie secondaire au saignement

chez les patient sans contre-indications

programmé pour une chirurgie?



Délibération Conférence de Paris - Traité de Versailles 1919

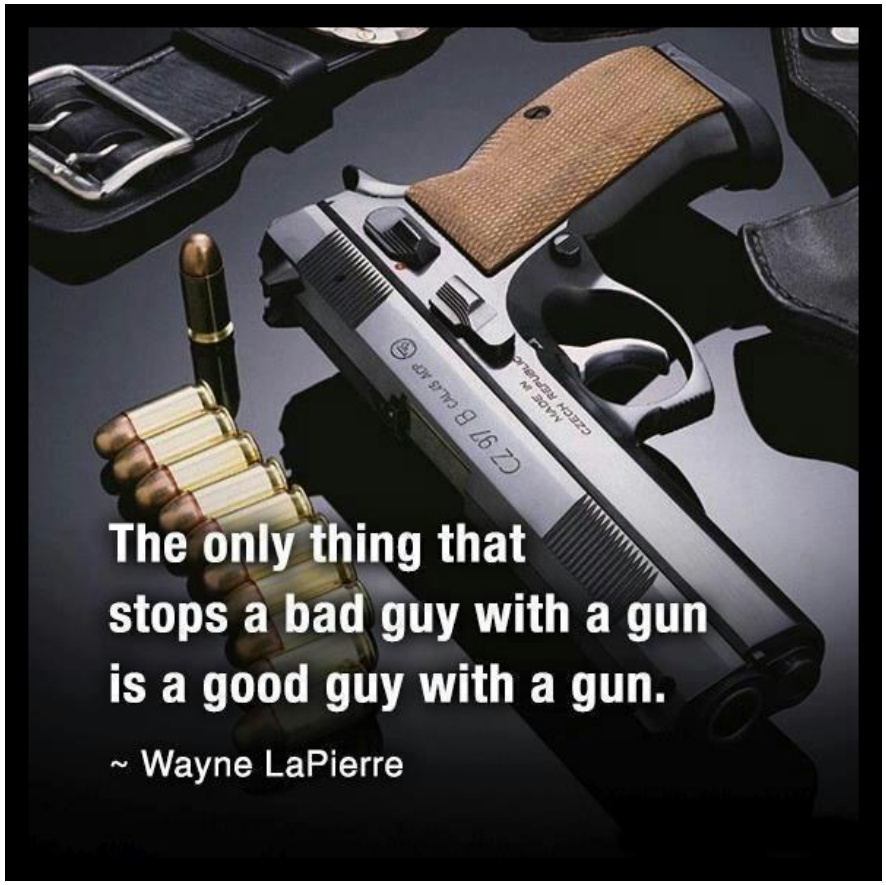
Délibération du jury

NOUVELLES ÉVIDENCES

1. *M.A.R.C.O.*
    1. *MÉTA-ANALYSE 1235 patients admis pour chirurgie recevant HES*
    2. *Pas de différence mortalité et atteinte rénale*
2. *ARISCAT*
    1. *banque de donnée prospective 2462 patients de chirurgie générale*
    2. *Pas de différence mortalité*
3. *Zampieri*
    1. *Étude retrospective 385 patients chirurgie oncologique*
    2. *Pas de différence mortalité*
4. *RAFTING sous-groupe chirurgical*
    1. *Pas de différence de mortalité*
5. *PASS*
    1. *1130 patients pédiatriques admis pour chirurgie*
    2. *Dose < 20ml/Kg*
    3. *Pas de différence de mortalité*

Risques versus bénéfices pour le patient

Qui est le coupable?



Le HES 130/0,4 ou celui qui l'utilise (inadéquatement) …

Michael Jackson tué par le Propofol.

Paris Match 26 juin 2010

Horaire

Pharmaco 2018

Date	Heures	Titre du cours	Professeur	Endroit
13 septembre 2018	14h - 15h	Introduction à la pharmacologie de l'anesthésie	Jean-Sébastien Lebon	ICM Auditorium (C-1890)
	15h - 16h	Introduction à la pharmacogénomique	Simon Dedenus	
20 septembre 2018	14h - 17h	Pharmacocinétique / pharmacodynamie	Résidents	ICM Auditorium (C-1890)
27 septembre 2018	14h - 17h	Agents volatils	Jean-Sébastien Lebon	ICM Auditorium (C-1890)
04 octobre 2018	14h - 17h	Anesthésiques locaux	Ariane Clairoux	HMR
11 octobre 2018	14h - 17h	Pharmacologie SNA	Alain Deschamps	ICM Auditorium (C-1890)
18 octobre 2018	14h - 17h	Curares, antagonistes et monitoring NM	Louis-Philippe Fortier	HMR
25 octobre 2018	14h - 17h	Agents d'induction intraveineux	Christian Ayoub	ICM Auditorium (C-1890)
1 novembre 2018	14h - 17h	Pharmacologie Vasculaire	Dominique Lafrance	CHUM
8 novembre 2018	14h - 17h	Pharmacologie de la douleur et opiacés	Anh Nguyen	HMR
15 novembre 2018	14h - 17h	Pharmacologie du patient âgé	Pierre Beaulieu	CHUM
22 novembre 2018	14h - 17h	Autres analgésiques (AINS, adjuvants)	Anh Nguyen	HMR
6 décembre	15h - 17h	**EXAMEN**	Jean-Sébastien Lebon	ICM (C-3430)

Version 4.0 - 2016

- Intégration des différents cours pour éviter les répétitions
- Distribution du National Curriculum aux professeurs pour assurer la couverture complète des objectifs d'apprentissage sur les différents sujets.
- Ajouts des cours suivants:
  - Curares
  - Pharmacologie vasculaire
  - Pharmacologie SNA
  - Phamacologie du patient agé
- Modification de l'examen

Version 4.0 - 2018

- En route vers le meilleur cours de l'histoire de pharmacocinétique de l'histoire de l'anesthésie…
  - Un sujet par résident.
  - Présentation de 4 minutes avec un maximum 5 diapositives
  - 1 exemple clinique adapté à l'anesthésie par sujet

  - **Pharmaco Jeopardy** – 11 octobre
    - Gars contre filles
    - Bière et vin au bar Le Rosemont après la partie
    - Gagnants (es) sont invités (es)

Pharmacocinétique

Résident	Sujet
Catherine BERGERON	ABSORPTION – Oral et rectal
Jean-François GAGNÉ	ABSORPTION – IM et SC
Mellisande BOUDREAULT	ABSORPTION – Intraveineux et autres voies
Marie-Ève BOISSELLE	DISTRIBUTION – Volume de distribution central et périphérique
Maxime CARON-GOUDREAU	DISTRIBUTION – Distribution Passive, Transport actif et diffusion facilitée
Geneviève LACHANCE	ÉLIMINATION – Clairance hépatique
Philippe CHAMPAGNE	ÉLIMINATION – Cytochrome
Marjorie COUTURE	ÉLIMINATION – Clairance rénale
Jennifer PALERMO	ÉLIMINATION – Clairance tissulaire
Marie-Pierre GAGNÉ	ÉLIMINATION – Métabolisme : Biotransformation (phase 1) et conjuguaison (phase 2)
Remy DAMPHOUSSE	CINÉTIQUE – Temps de demi-vie et volume de distribution
Héloïse POULIN	CINÉTIQUE – Temps de demi-vie contextuel
Julianne GUAY	CINÉTIQUE – Ordre 0 vs ordre 1
Sarah MAXIMOS	CINÉTIQUE – Modèle unicompartimental et multicompartimental

Pharmacodynamique

Résidents	Sujets
Christophe SALOIS	INTERACTION LIGAND-RÉCEPTEUR – Agoniste, antagoniste et synergisme
Élizabeth LAROCHELLE	INTERACTION LIGAND-RÉCEPTEUR – Agoniste partiel et agoniste inverse
Maxim SOUCY-PROULX	TYPE DE RÉCEPTEURS – Protéine G et canaux ioniques
Nicolas SAUTHIER	ÉVALUATION DE L'EFFET CLINIQUE – Relation dose - réponse
Jason McDEVITT	ÉVALUATION DE L'EFFET CLINIQUE – Fenêtre thérapeutique
Simon VILLENEUVE	ÉVALUATION DE L'EFFET CLINIQUE – Tolérance et tachyphylaxie
Virginie SBEGHEN	INTÉRACTIONS MÉDICAMENTEUSES – Même récepteur
Anthony SULTAN	INTÉRACTIONS MÉDICAMENTEUSES – Différents récepteurs

Programme anesthésiologie -Université de Montréal
Année académique 2018-2019

- CPC
- Programme de support par les pairs
- ATLS
- Programme de formation en échographie ciblée
- Programme de préparation pour les examens oraux CR
- Refonte des CSB
- Visite interne