

# Febrile Non-haemolytic Transfusion Reactions

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# As many questions as answers

- Pathophysiology?
- Frequency following prestorage leucodepletion?
- How to define them -  $>1^{\circ}\text{C}$  or  $>1.5^{\circ}\text{C}$ ?
- Relationship to antibodies against low frequency antigens
- Relationship to TRALI?
- Always harmless?
- Should we do more bacterial cultures?
- When do we report them to SABRE?

# White cell contamination of red cells

- Leucocyte antibody in patient's plasma reacting with leucocytes in the component, with release of pyrogens causing fever
- Payne R Leucoagglutinins in 41% patients  
Vox Sang 1957
- Menitove JE Prevention of >80% reactions by leucocyte reduction to  $<5 \times 10^8$ . Vox Sang 1982

# White cell contamination of platelets

- Leucocyte derived cytokines released on storage
- Probably largely from lymphocytes, ? some from monocytes

# Cytokines in stored platelet concentrates

Muyllé et al Transfusion 1993, 33, 195-99

12 PC-PRP	Storage time (days)				
	0	1	3	5	7
TNF- $\alpha$ ng/L	7 $\pm$ 3	9 $\pm$ 2	282 $\pm$ 569	571 $\pm$ 710	623 $\pm$ 719
IL -1 $\beta$ ng/L	76 $\pm$ 51	121 $\pm$ 141	771 $\pm$ 1695	5253 $\pm$ 8154	5155 $\pm$ 6822
IL-6 ng/L	<4	4.3 $\pm$ 12.0	1293 $\pm$ 3015	4883 $\pm$ 6064	6492 $\pm$ 7241

# Cytokines in platelet concentrates

Heddle Curr.Opin Haem 1999 420-430

Cytokine pg/ml Day 5	PC-PRP	PC-BC	PC-aph
IL-1 $\beta$	30-5253	<4-76	1.7
IL-6	43-4883	0-78	7
IL-8	907-32438	<3-440	<3

# Pathophysiology of FNHTR

## Numerous other explanations

- Donor white cells
- Cytokine content of component – leucocyte or platelet derived
- Donor antibodies – HLA and granulocyte specific antibodies
- Patient antibodies – HLA, granulocyte and platelet specific antibodies
- Patient potential for cytokine release – underlying condition, genetic factors

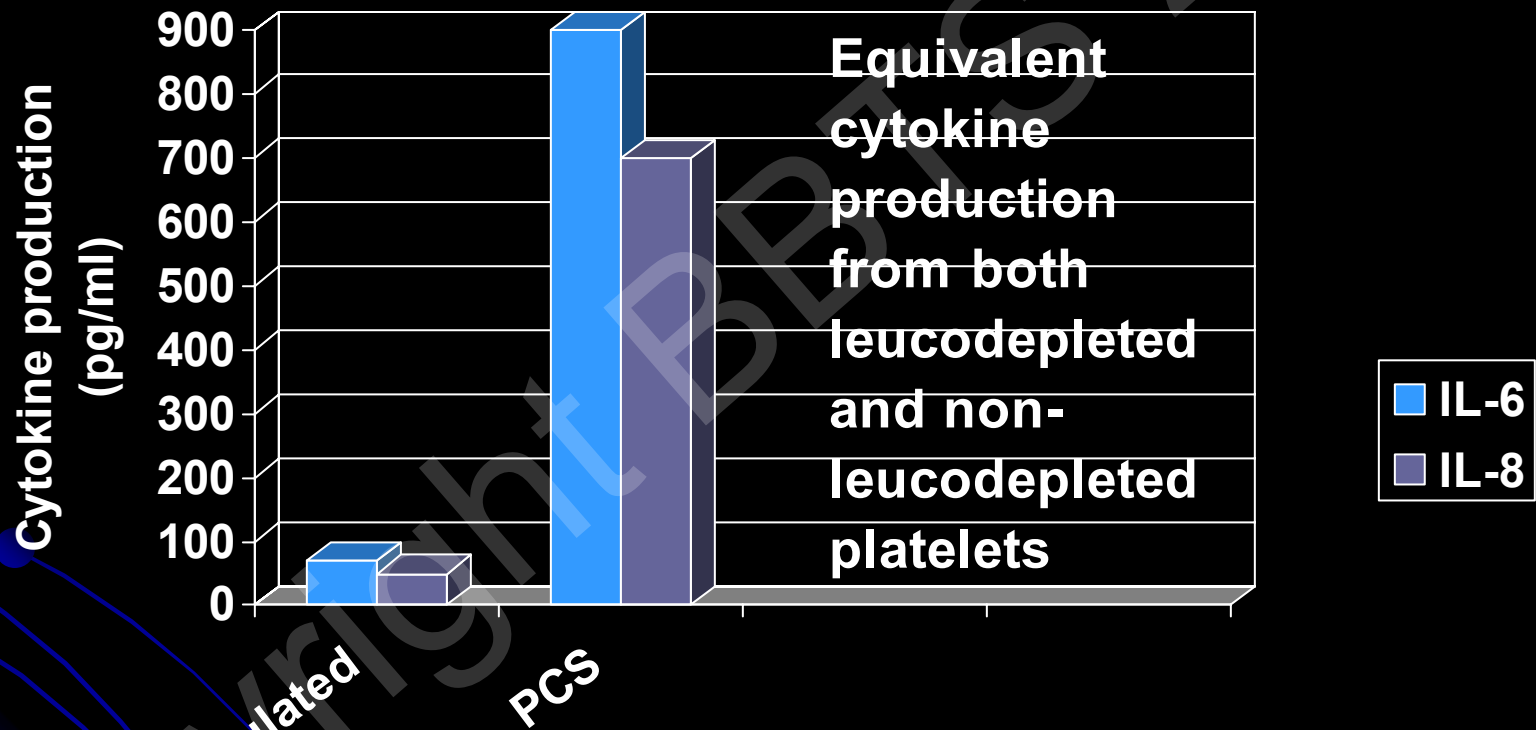
# CD40-CD154 (CD40 ligand) pathway

- B lymphocyte immunoglobulin class switching
- Activation antigen presenting cells
- T cell activation

# Platelet derived cytokine CD40-CD154 (CD40 ligand) pathway

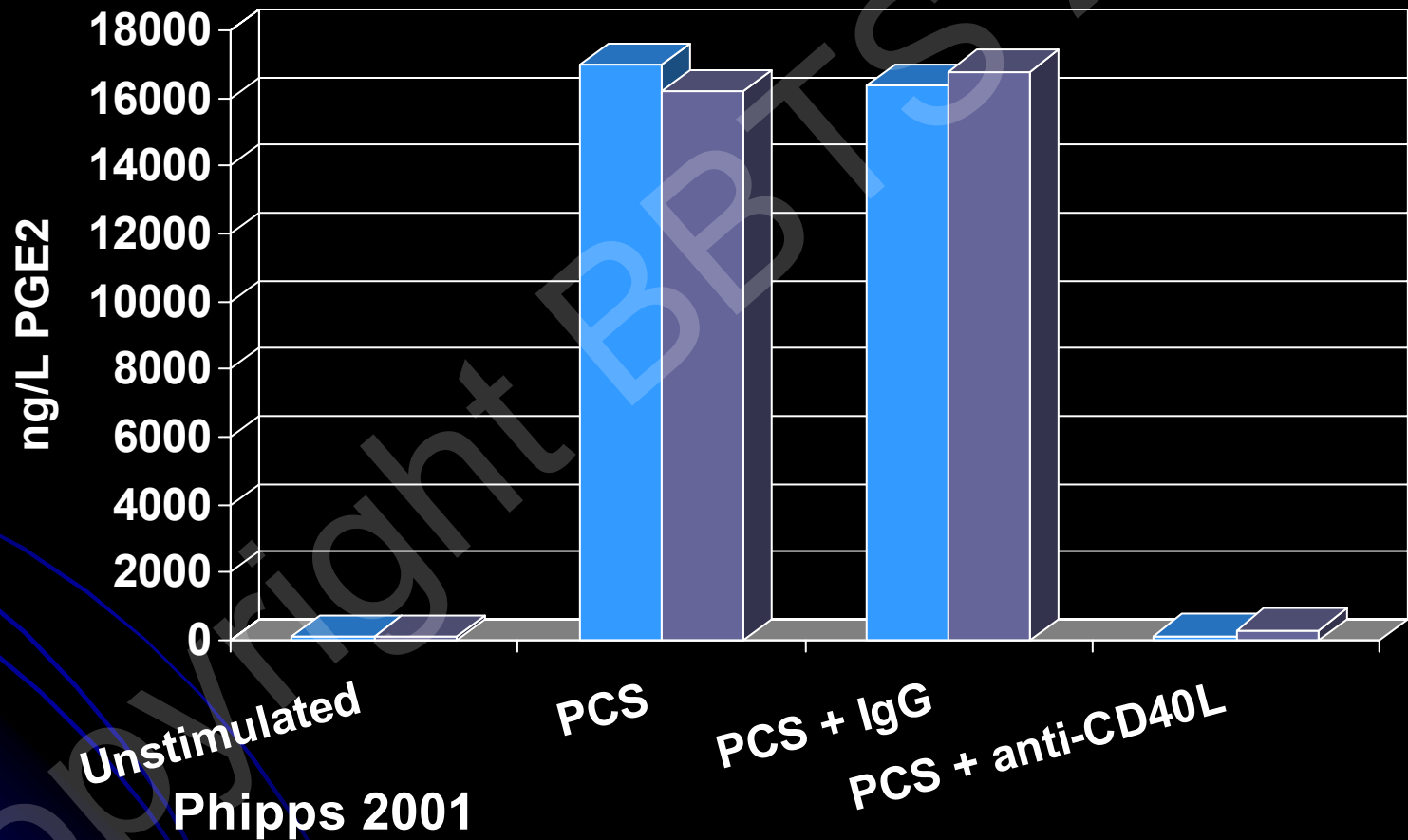
- Platelets contain preformed CD40L
- CD40 ligand expressed and expelled after activation
- Activation of structural cells eg endothelium to produce cytokines, express cyclo-oxygenase-2 and produce PGE2
- Prostaglandin E2 – key producer of fever in man
- Amounts CD40L in platelet concentrate supernatant day 5, 3000 – 7000ng/L (comparable concentrations to those found in serum in chronic inflammation)

# Effect of platelet concentrate supernatant on cytokine production human lung fibroblasts



Blumberg 2003

# PGE2 production in 2 strains of human lung fibroblasts by CD40L in PCS



Phipps 2001

# Association CD40L (CD154) with platelet reactions – Blumberg 2006

- 534 platelet transfusions
- Measured PC supernatant IL-6, IL-8, MCP-1, sCD40L, RANTES
- 10/534 febrile and 4/534 allergic reactions
- Febrile reactions:
  - IL-6 2.3 fold higher p=0.005
  - IL-8 2.2 fold higher p=0.001
  - MCP-1 2.6 fold higher p=0.002
  - sCD40L 1.25 fold higher p=0.03
- Summed levels of mediators; reaction rates increased 1 to 7% from first to fifth quintile
- 93% transfusions with highest levels of mediators did not lead to a reaction
- All but one reaction in patients with haematological malignancies

# Association cytokine gene polymorphisms with FNHTR in multitransfused patients

Addas-Carvalho T Med. 2006, 16, 184-91

- 2 populations of patients
  - FNHTR after <20 transfusions
  - No FNHTR despite >20 transfusions
- Polymorphisms IL1B, IL6, IL10, TNF
- Association IL1RN\*2.2 genotype with occurrence previous FNHTR ( $p < 0.025$ )

# Donor and Patient antibodies

Matsuyama Transfusion 2008, 48, 1526-1527

- 85 cases of NHTRs
- TRALI 9
- Possible TRALI 6
- Dyspnoea 37
- Dyspnoea and hypotension 18
- Hypotension 9
- Anaphylactic 6
- Donor samples 66

# Patient antibodies

Matsuyama Transfusion 2008, 48, 1526-1527

- HLA antibodies
  - 26% patient samples
  - 6% donor samples

# Non-HLA antibodies

Matsuyama Transfusion 2008, 48, 1526-1527

Neuts	Monos	CD4+	CD20+	Plts	Patients	Donors
+	-	-	-	-	9	11
+	+	-	-	-	4	1
+	+	+	-	-	1	0
+	+	-	-	+	4	0
+	+	-	+	+	4	0
+	-	-	+	-	1	0
-	-	-	+	-	4	0
-	-	-	-	+	2	0
Total					29	12

# Effect of prestorage leucodepletion on FNHTR

## Paglino et al Transfusion 2004

Component	No. patients transfused	%FNHTR	% allergic
RBC control	2849	0.34 ± 0.15	0.09 ± 0.07
RBC Id	11184	0.18 ± 0.10	0.09 ± 0.07
p value		<0.0001	0.69
Rel. decrease (%)		47.1	0

# Effect of prestorage leucodepletion on FNHTR

## Paglino et al Transfusion 2004

Component	No. patients transfused	% FNHTR	% allergic
PC-BC control	1120	0.49 ± 0.58	0.10 ± 0.12
PC-BC Id	2322	0.35 ± 0.42	0.09 ± 0.11
p value		0.23	0.69
Rel. decrease (%)		28.5	10

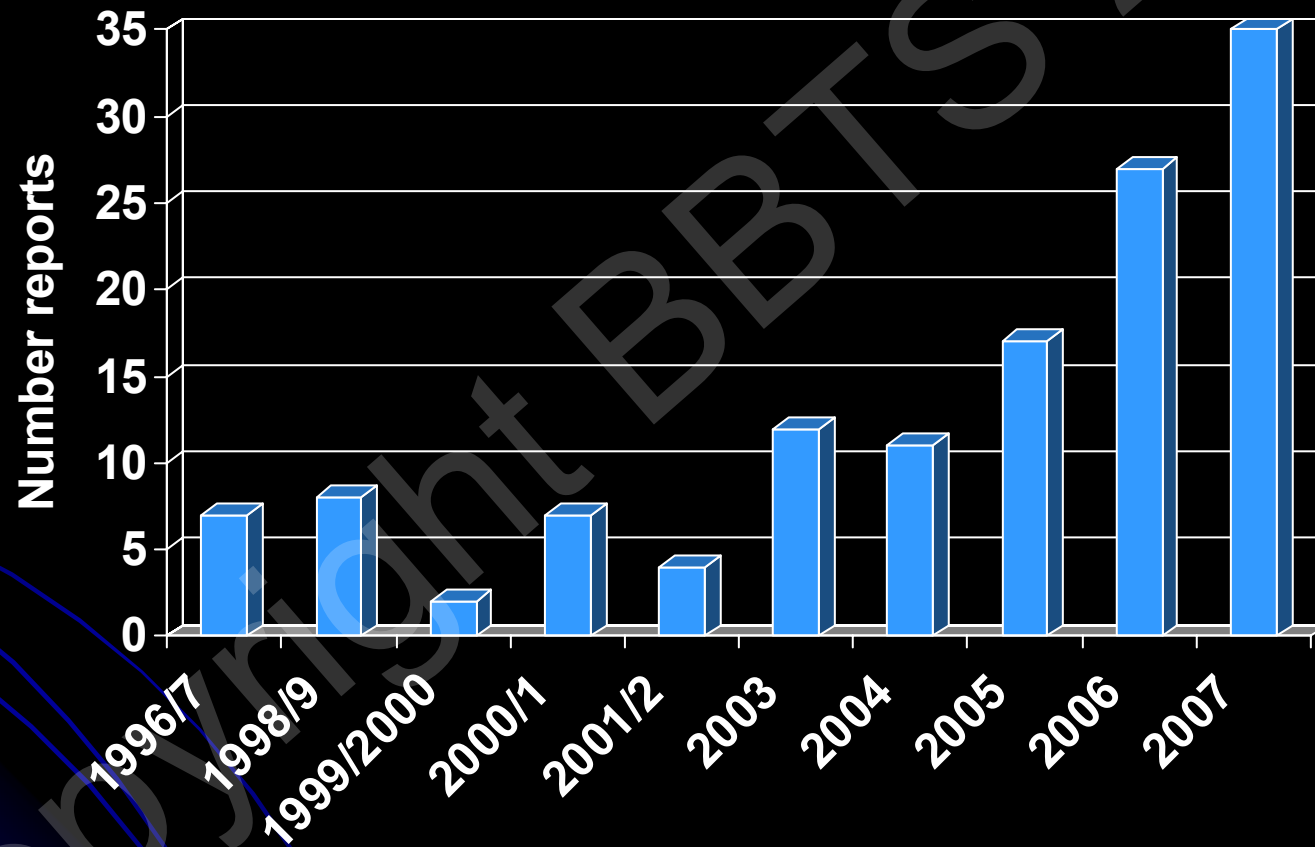
# Other studies

Author	Component	(Benefit) FNHTR
Uhlman	RBC	0.12 to 0.08%
Yazer	PC	None
Landmark	All	0.33 to 0.17%
French	RBC	41% decrease
Pruss	SDAP	0.11%
	FFP	0.02%

## So...in the UK

- Assuming 0.1% FNHTR
- 2235 reports from RBC
- 255 reports from platelets
- Wisdom of SHOT!

# FNHTR reported to SHOT



# Breathlessness with HLA Class II antibody containing plasma

- Sakagawa – Transfusion 2007
- 81yr male – NHL, PC-aph.
  - Chills, tachycardia, lumbar pain, followed by fever
  - Dyspnoea, O2 sats 70%, CXR clear
- Donor serum – HLA-DR antibodies including DR13 (recipient's HLA-DR type)
- Crossmatch patient's lymphocytes v donor plasma positive
- Treatment DR13 pos mononuclear cells with donor plasma caused cytokine secretion

# Neutrophil-specific antibodies and leucopenia and pulmonary reactions

- **Fayadi et al Transfusion 2007**
  - Apheresis donor with anti-HNA-2a
  - 27 donations of platelets
  - 39 separate transfusions
  - 12 transfusion reactions in 9 patients – immediately or within 2.5 hours
  - 9/12 reactions involved mild to moderate pulmonary symptoms
  - 9/12 associated with leucopenia

# Spectrum of pulmonary reactions with transfusion of neutrophil specific antibodies - Fayadi et al

Case	Diagnosis	Symptoms	Pre - WCC	Post - WCC
1	ALL	Dyspnoea	1.93	0.544
2	PBPC transplant	Chills, dyspnoea, hypertension	4.8	0.9
3	PBPC transplant	Chills, agitation, hypertension, cyanosis	14.8	15.7
4	SAA	Fever, chills, rigors, wheezing, hypertension 15 minutes later	3.8	0.5
5	Melanoma	Fever, chills, rigors, cyanosis	1.4	1.5
6	SAA	Fever, chills, dyspnoea, rigors 20 minutes later	0.4	0.05

# A touch of TRALI – 3 case reports

Davis Transfusion 2008, 48 541-545

Component	FFP x 2, RBC x 1
Initial symptoms	Chills, dyspnoea
Temperature rise	+ 1.8 – 2.2°C
O2 sats	88 – 92%
Change in other obs	?
Examination	No stridor, wheeze, rales or urticaria
Donor	HLA Class I antibodies

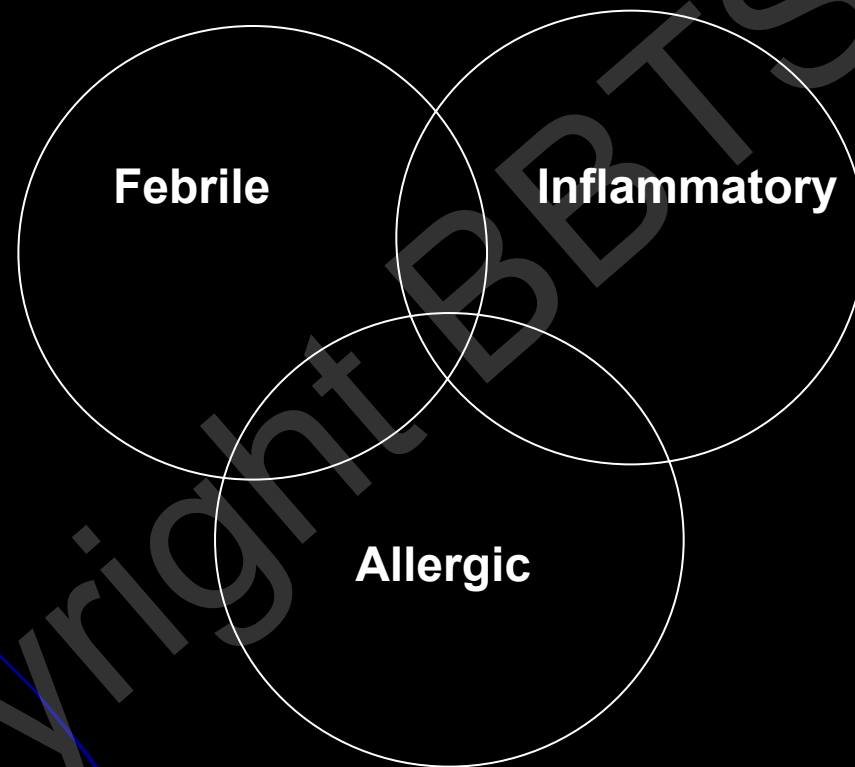
# SHOT 2006 – symptomatic febrile reactions

Comp.	Dyspnoea (sats%)	BP	Symptoms	Investigations
PC	85	Increase		MCT - N
PC	x	Increase	Myalgia/ chest pain	x
RBC	x	Fall	Myalgia/ chest pain	x
RBC	√		Myalgia, vomiting	IgA - N
RBC	82	Fall	Myalgia, vomiting	x
RBC		Increase	Myalgia	HLA ab
RBC	72		Myalgia, nausea	x
RBC	87		Myalgia	MCT - N

# Problems with definitions acute transfusion reactions – Sanders et al Transfusion 2007

- Reviewed 595 acute transfusion reactions
- Had 25 categories eg:
  - Allergic and/or febrile
  - Probable allergic and/or febrile
  - Allergic vs. anaphylactoid
  - Possible allergic vs. vascular vs. haemolytic
- Yet..... 22% could not be unequivocally interpreted

# The overlap of FNHTR



# Sanders et al

Category/ severity	1	2	3	4 (5 = death)
Febrile asymptomatic	>1°C <39°C No other symptoms	39 – 40°C No other symptoms	Max >40°C <24 hours	>40°C >24 hours
Inflammatory	Mild rigors ± chills ± fever, mild discomfort	Moderate, discomfort requiring analgesia	Severe, hypotension	Shock
Allergic	Transient flushing or rash	Rash, urticaria, dyspnoea	Bronchospas- -m, oedema ± hypotension	Anaphyla- -xis ± shock
Mixed allergic and/or inflammatory	Any combination			

# Febrile reactions and antibodies against low frequency antigens

- 2005 – anti-Wra, anti-Bga
- 2006 – 1 case of undetermined specificity
- 2006 – anti-Wra, anti-Rogers
- No haemolysis but fever, rigors, chills
- Coincidence (4.3% donors have anti-Wra) or related?

# FNHTR – usually harmless

- SHOT reports
- 2004 – 97 yr. male with fever, rigors, myalgia and hypotension developed acute coronary insufficiency
- 2005 -74yr. Male with similar symptoms required overnight admission with chest pain and agitation

# Bacterial contamination

- NBS contamination rate of time-expired platelets
  - 0.7% pools
  - 0.4% apheresis
- Reported serious bacteraemia - SHOT
  - 1 in 100,000 for platelets
  - 1 in  $\pm 5 \times 10^6$  for red cells

# Perez P. French BACTHEM study

- 158 suspected cases of bacteraemia
- 41 confirmed: 25 RBC, 16 PC
- Comparative risks v. receiving RBC for anaemia:
  - RBC for pancytopenia OR 7.3
  - PC for pancytopenia OR 4.5
  - Immunosuppression OR 2.8

# Risk in bone marrow transplant recipients

- Chin E. Transfusion 2004
- Prospective study of symptomatic bacteraemia following platelet transfusion
- 3584 platelet transfusions
- 161 patients – post-BMT
- Trigger for investigation
  - Rise in temperature  $>2^{\circ}\text{C}$
  - Rise in temperature  $>1^{\circ}\text{C}$  with chills/rigors

# Chin E. Transfusion 1994

- Bacteraemia – isolates from bag and patient with identical profiles
- 37 febrile reactions
- 10/37 bacteraemias – 27% chance
- If fever  $>2^{\circ}\text{C}$  – 42% chance
- Septic shock in 4/10

# Reporting to SABRE

? Need to use a version of Sanders et al

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