BLOOD TRANSFUSION
&
NECROTISING ENTEROCOLITIS

Is there a causal link?

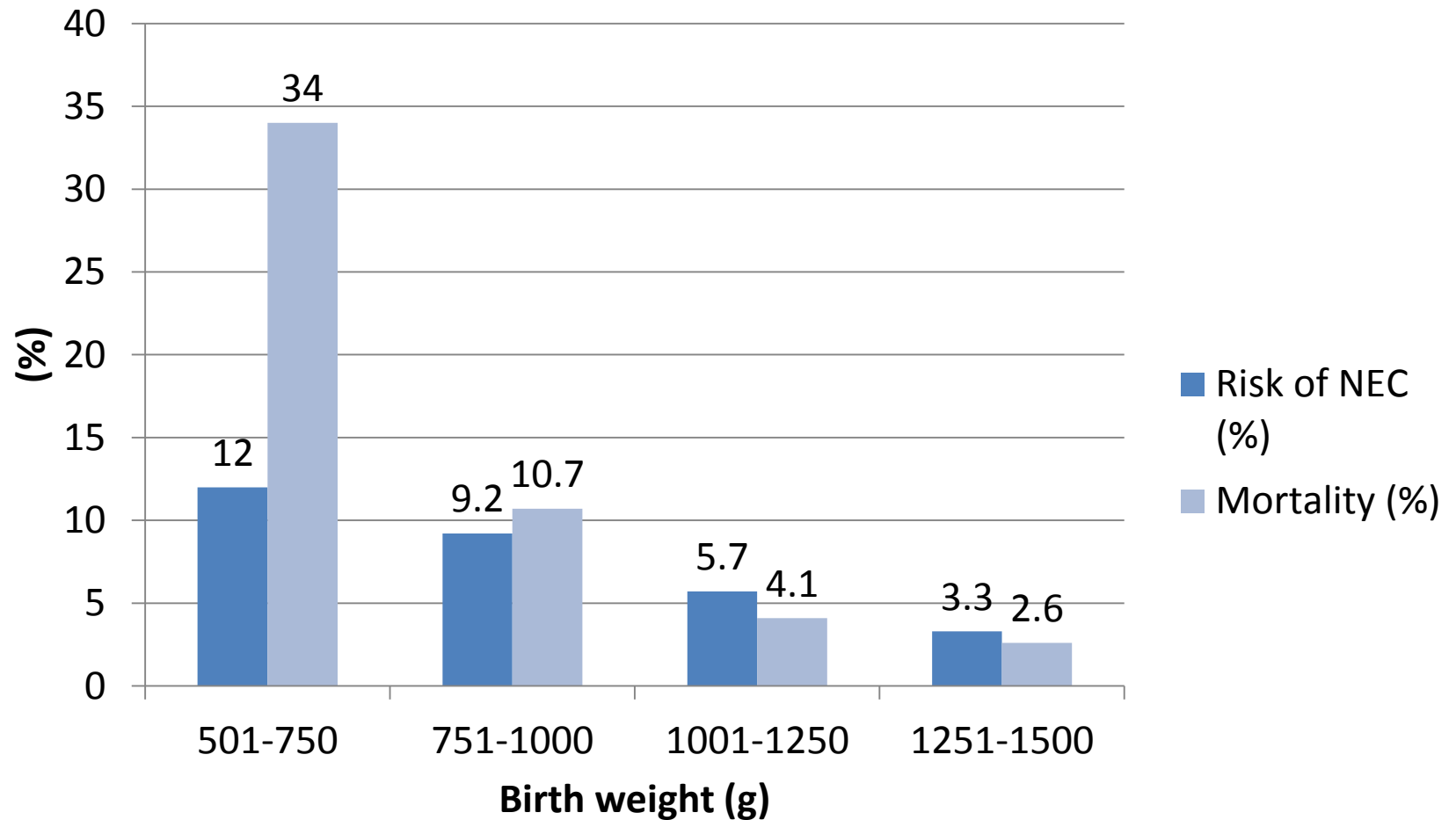Amit Gupta

NEC

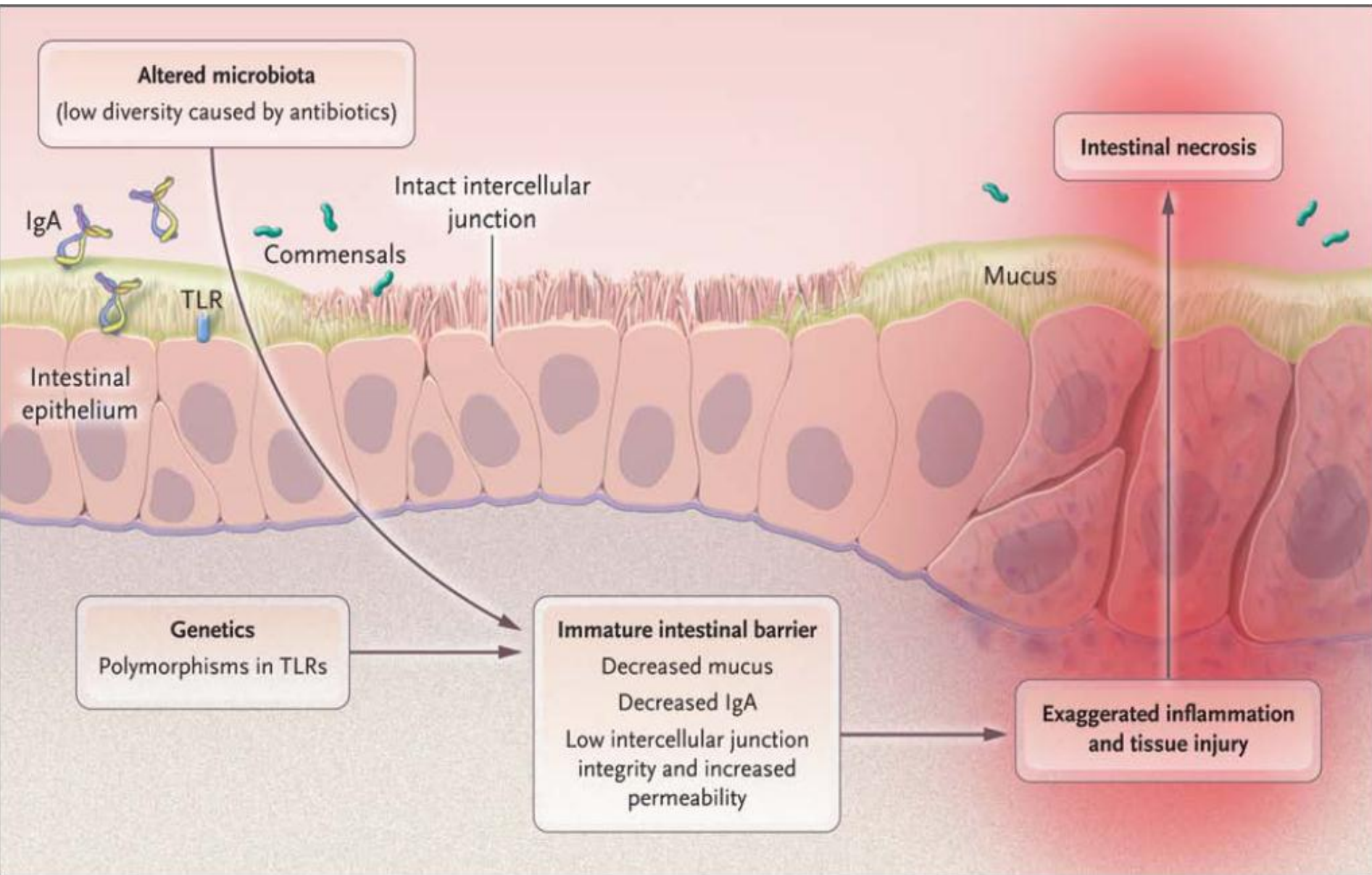- Mean prevalence of the disorder is about 7% among infants with a birth weight < 1500g

- Mortality : 20% to 30%

1. Fitzgibbons et al. 2009. J Ped Surg   *2. Neu et al. 2011. NEJM*

NEC epidemiology

Fitzgibbons. J Pediatr Surg 2009

Altered microbiota
(low diversity caused by antibiotics)

IgA

Commensals

TLR

Intact intercellular junction

Intestinal epithelium

Mucus

Intestinal necrosis

Genetics
Polymorphisms in TLRs

Immature intestinal barrier
Decreased mucus
Decreased IgA
Low intercellular junction integrity and increased permeability

Exaggerated inflammation and tissue injury
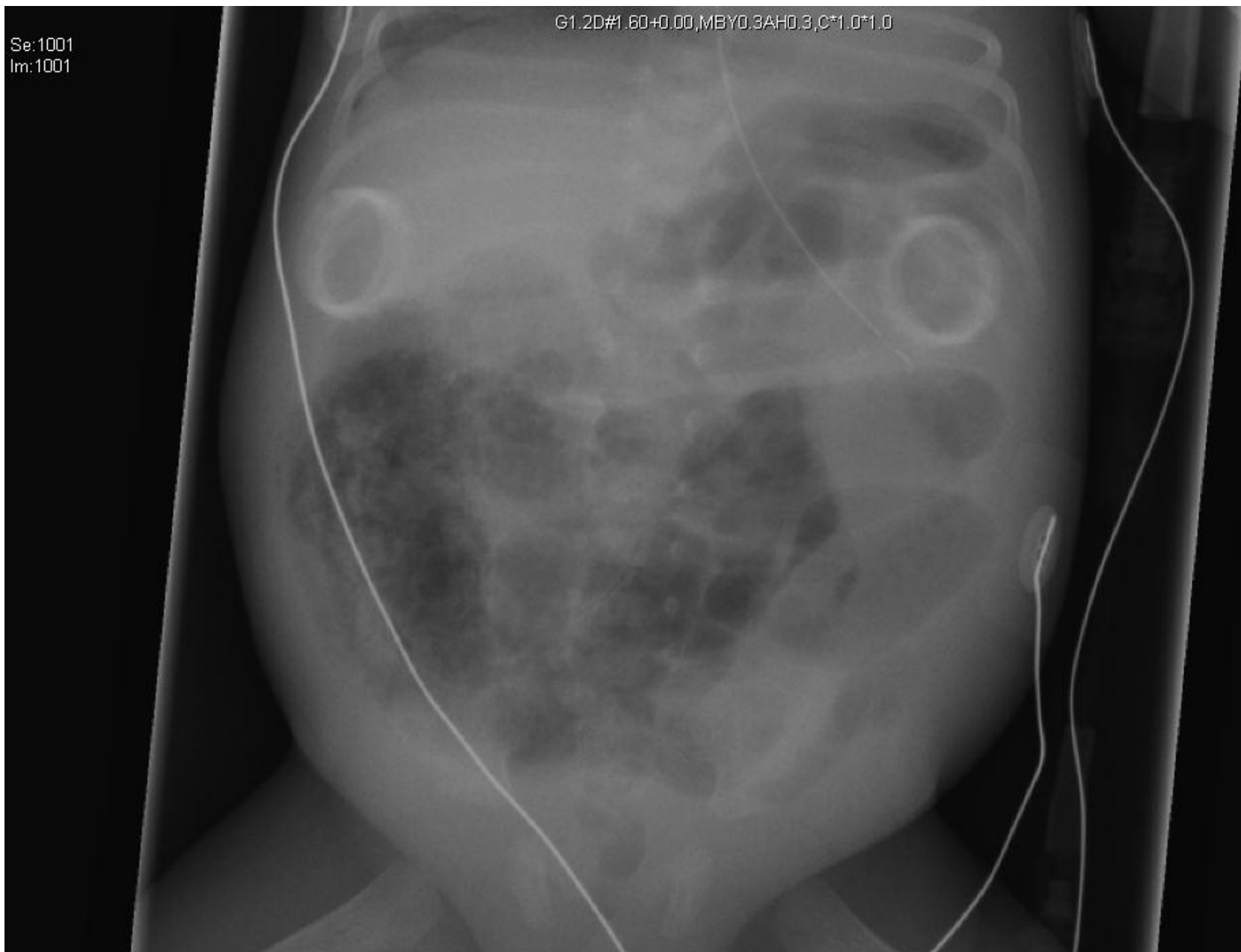
Neu et al. 2011. NEJM

Baby J

- Day 35
- Anemic – Hb 7.1 g/dL
- Few desaturations
- CRP =2, no other concerns
- Transfused – 15 mL/kg of packed cells
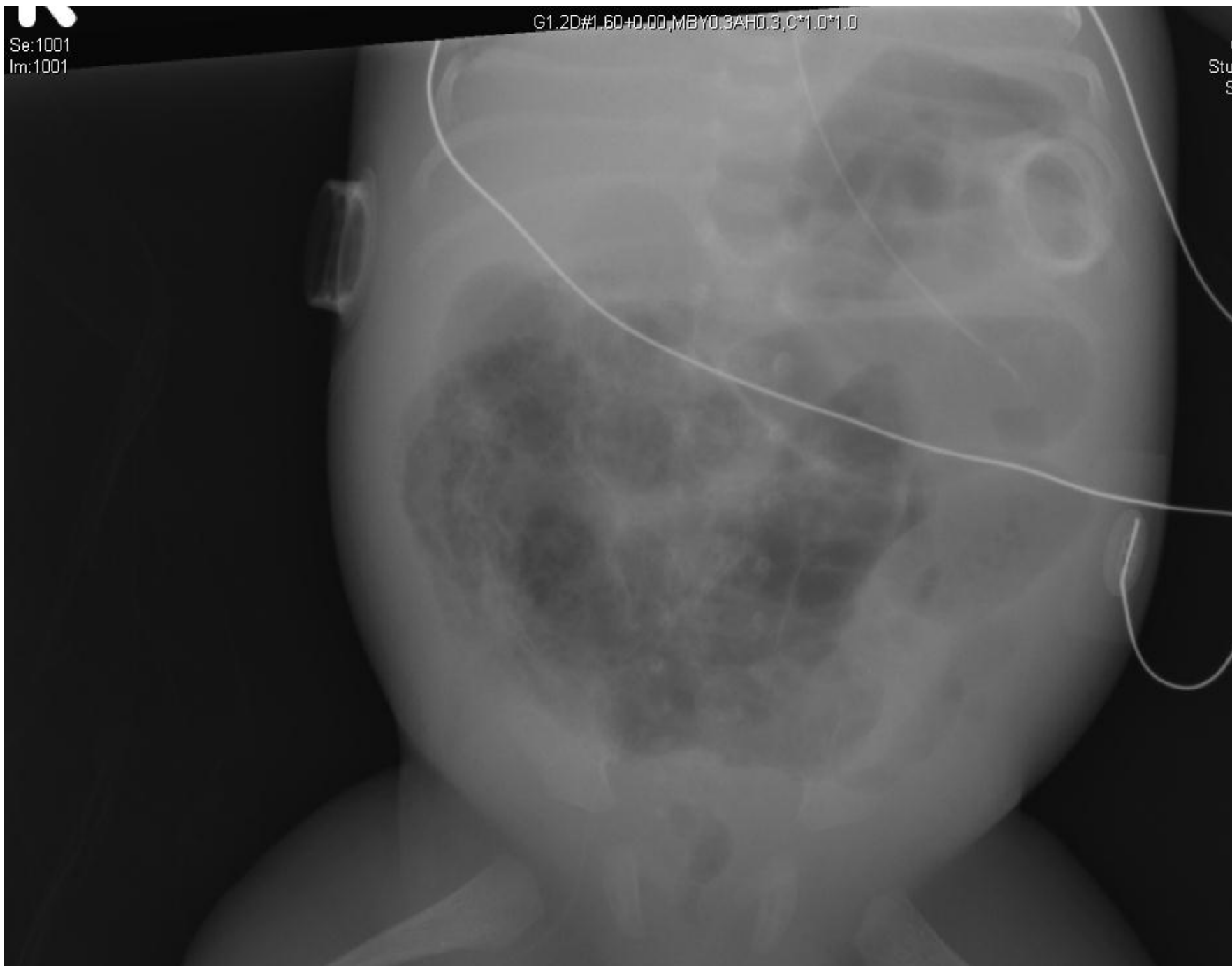- Within 5 hours – profoundly unwell
- Distended abdomen

G1.2D#1.60+0.00,MBY0.3AH0.3,C*1.0*1.0

Progress

- Rapid progression to shock
- Multi organ failure
- Died within 24 hours of onset of NEC
- Post mortem: Extensive necrosis of almost the entire gut

NEC and blood transfusion

- Oklahoma outbreak– 1987

- 33 babies had NEC over a 6-month. Risk factors compared with 37 controls

- Significant association of blood transfusion and NEC with an odds ratio of 15.1 (95% confidence interval [CI], 2.6-92.5)

- Outbreak ended without any change in practice

G.A. McGrady, P.J. et al . Am J Epidemiol 1987

10 years later

- Transfusion practice and NEC - 6 neonatal units
- Multivariate analysis

  – Two "high transfusion units" transfused 70mL/kg more RBC than the two "low transfusion units".

  – NEC in 7% in the high-transfusing NICUs (adjusted OR, 1.1; 95% CI, 0.5-2.2)

  – NEC in 2% in the low-transfusing NICUs (adjusted OR, 0.3; 95% CI, 0.1-0.8;)

Bednarek FJ, et al . Pediatrics 1998

Pathogenesis of transfusion related acute gut injury

- Immune
- Anemia
- Age of blood products
- Vascular

Immune – double hit

- Transfusion related acute gut injury
  - Two hit model[1]
  - Transfusion of response mediators (HLA, neutrophil antigen, red cell fragments, cytokines)[2] lead to an exaggerated response
  - Exaggerated intestinal immune response similar to TRALI observed in adult

- Transfusion leads to activation of T-cell antigen on RBCs – low grade hemolysis – linked to NEC

1. Silliman et al. Blood Rev 2009   2. Lee J et al. Nat Med 2010

Anemia

- Anemia *per se* may be related to NEC

  - RBC transfusions can trigger GI injury in severely anemic patients on bypass[1]

  - Hemolytic disease of newborn, twin to twin transfusion, G6PD deficiency[2]

  - Severe anemia – high output cardiac state and restricted gut perfusion[3]

1. Huybregts et al. Aneth Anolg 2009   2. Schutzman et al. J Pediatrics. 2007   3. Alkaly AL et al. Pediatrics 2003

Stored blood

- Stored blood

  - Erythrocyte nitric oxide levels are depleted during storage, which can severely impair RBCs' hypoxic vasodilator activity[1]

  - Transfused RBCs could act as a nitric oxide sink, predisposing to vasoconstriction and ischemic insult[2]

1. Reynolds JD. Proc Natl Acad Sci USA 2007   *2. Gladwin MT. Curr Opin Hematol 2009.*

Vascular

- Doppler-blood flow in superior mesenteric artery

  – Normally increases following a feed
  – Fails to rise following a blood transfusion

Krimmel GA et al. Am J Perinatol 2006.

EVIDENCE SO FAR

Mally P et al. American J Perinatology 2006

- Retrospective study

- June 1999 to October 2000

- Single Centre

- NEC (stage 2+) cases divided into
  - Those receiving transfusion up to 48 hrs prior to developing NEC
  - No history of immediate transfusion
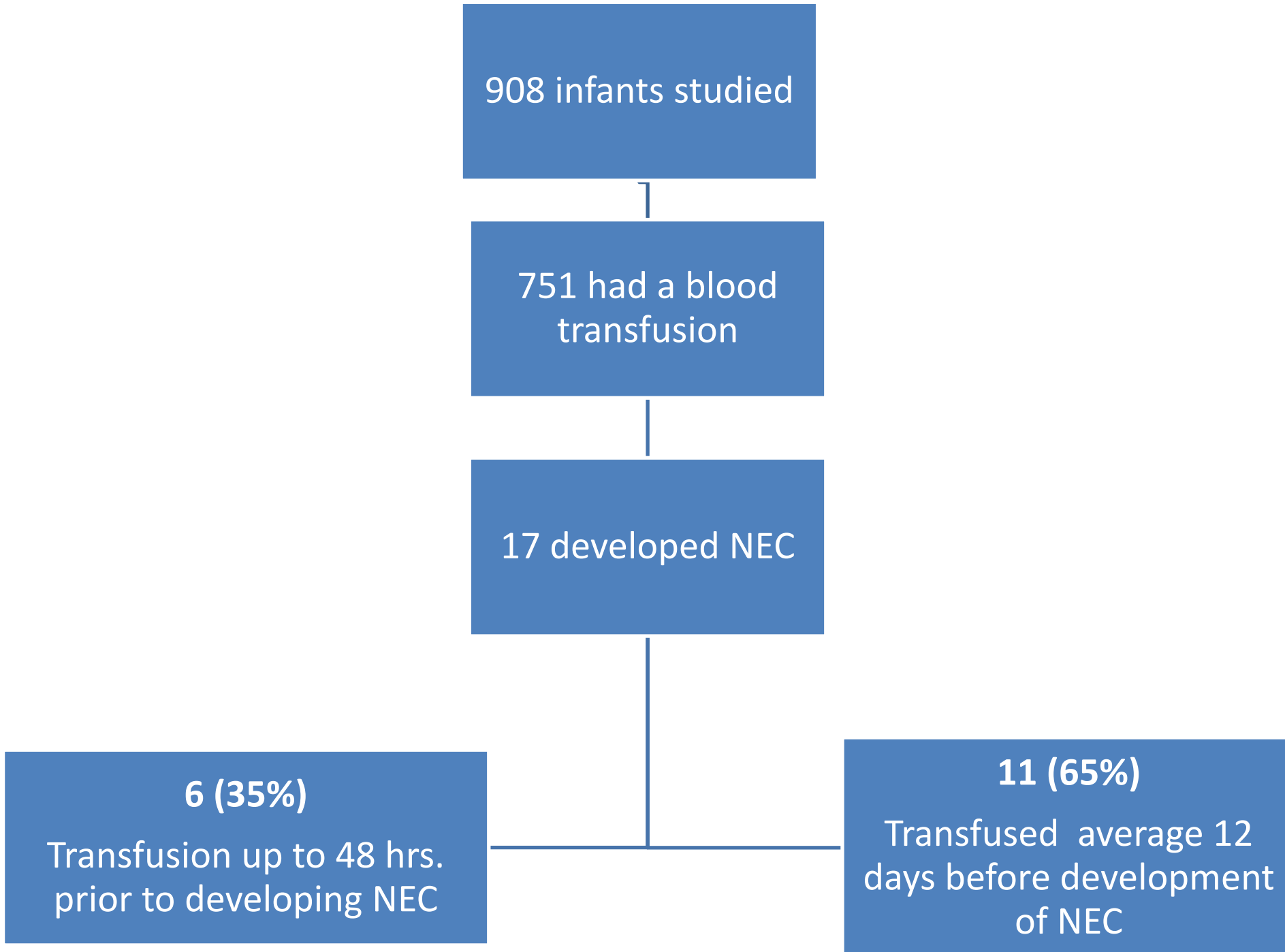
908 infants studied

751 had a blood transfusion

17 developed NEC

6 (35%)
Transfusion up to 48 hrs. prior to developing NEC

11 (65%)
Transfused average 12 days before development of NEC

Results

Transfusion associated – 6

- Post natal age 32 days*
- Signs 22 hours following transfusion*
- **Hematocrit : 24 (3)***
- Stable infants, growing, not ventilated, not septic

Non transfusion associated- 11

- Post natal age 15 days
- Signs 185 hours following transfusion
- **Hematocrit: 37 (7)**
- More often ventilated, 50% IV

* Significantly different
No difference in rates of PDA, use of indomethacin, IVH

Blau J et al. J Pediatr 2011.

- January 2007 to June 2008

- NEC : Bell stage 2+

- Indications for transfusion - unchanged

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                    ┌─────────────────────┐
                    │  256 VLBW infants   │
                    │     identified      │
                    │                     │
                    │    36 NEC cases     │
                    └─────────────────────┘
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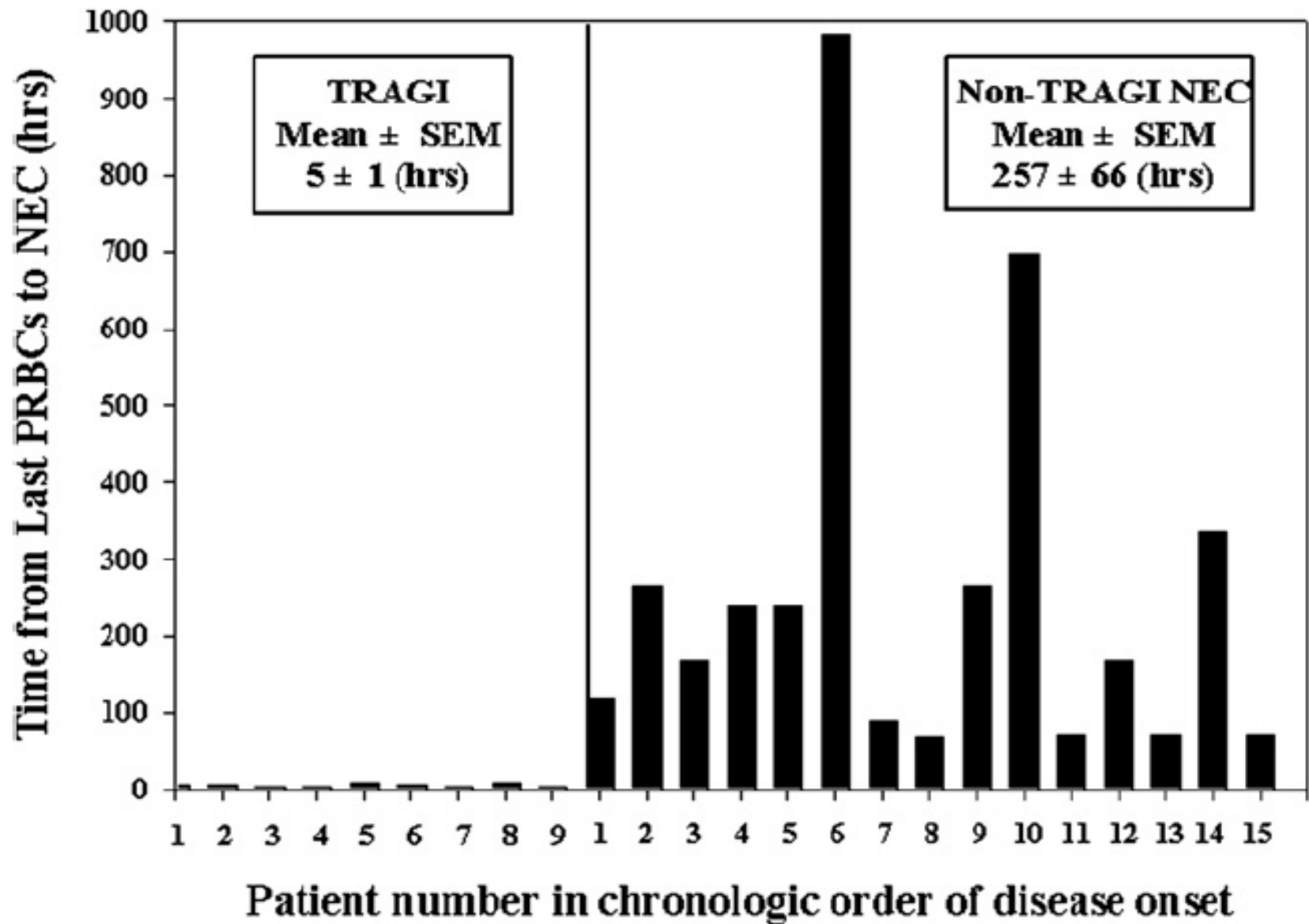

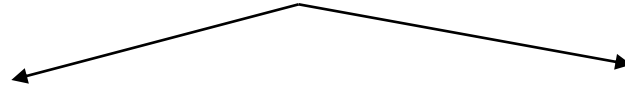| 9 (25%)
NEC associated with transfusion (48 hrs.) | 15
Non transfusion related NEC | 12
Never transfused NEC |

Temporal link: Time from last transfusion to development of NEC

NEC

Transfusion associated – 9   **Non transfusion associated- 15**

- Gestation 26 (0)wk*
- Postnatal age 30 days
- Signs 5 hours following transfusion*
- Hematocrit – 26*
- 83% NBM during transfusion
- 17% on EBM

- Gestation 27 (1) wk
- Postnatal age 30 days
- Signs 257 hours following transfusion
- Hematocrit – 33
- 69% NBM during transfusion
- 45% on EBM

* Significant difference
No difference in rates of use of breast milk, PDA, use of indomethacin, IVH

Compared to previous study

- NEC occurred even sooner after transfusion (average of 5 versus 22 hours)

- Antecedent severity of illness, though still relatively mild, was no longer just stable growing VLBW

- Postnatal age of infants in transfusion related NEC group was similar to non transfusion related NEC group

- The transfusion related NEC patients were more anemic (similar to previous study)

Case Control Study

Josephson CD et al- 2010

Josephenson et al – 2010

- All infants ≤ 34 w GA

- NEC stage 2 and 3

- Contemporary controls - matched for GA, admission date and birth weight

NEC

	Transfused n=47	Never transfused n=46
Gestation (wks), Median (IQR) *	25.9 (24-27)	30.7 (29-32)
Birth weight (g), Median (IQR) *	760 (660-950)	1415 (1180-1680)
Age at NEC, Median (IQR) *	37 (23-55)	13 (7-24)
Hct at NEC, Mean ± SD*	29.6 (5)	34.1 (9)
Ventilation just prior to NEC, n (%) *	9 (19)	1 (2)
PDA, n (%) *	16 (34)	2 (4)
Indomethacin, n (%) *	33 (70)	3 (6.5)

Frequency of PRBC transfusions was similar in NEC patients (51%) and controls (58%)

Early onset NEC vs. Late onset NEC

	Early Onset n=58	Late Onset N=35
Gestation (wks) *	30 w (27-32)	25.7 w (24-27)
Birth weight (g) *	1240 (960-1550)	735 (680-1005)
PDA *	3	15
Transfusion within 48 hours prior to NEC *	10 (26.7)	8 (47%)

Adjusted risk of NEC related to transfusions: odds ratio 14.5 (95% CI, 4.8,43.6)
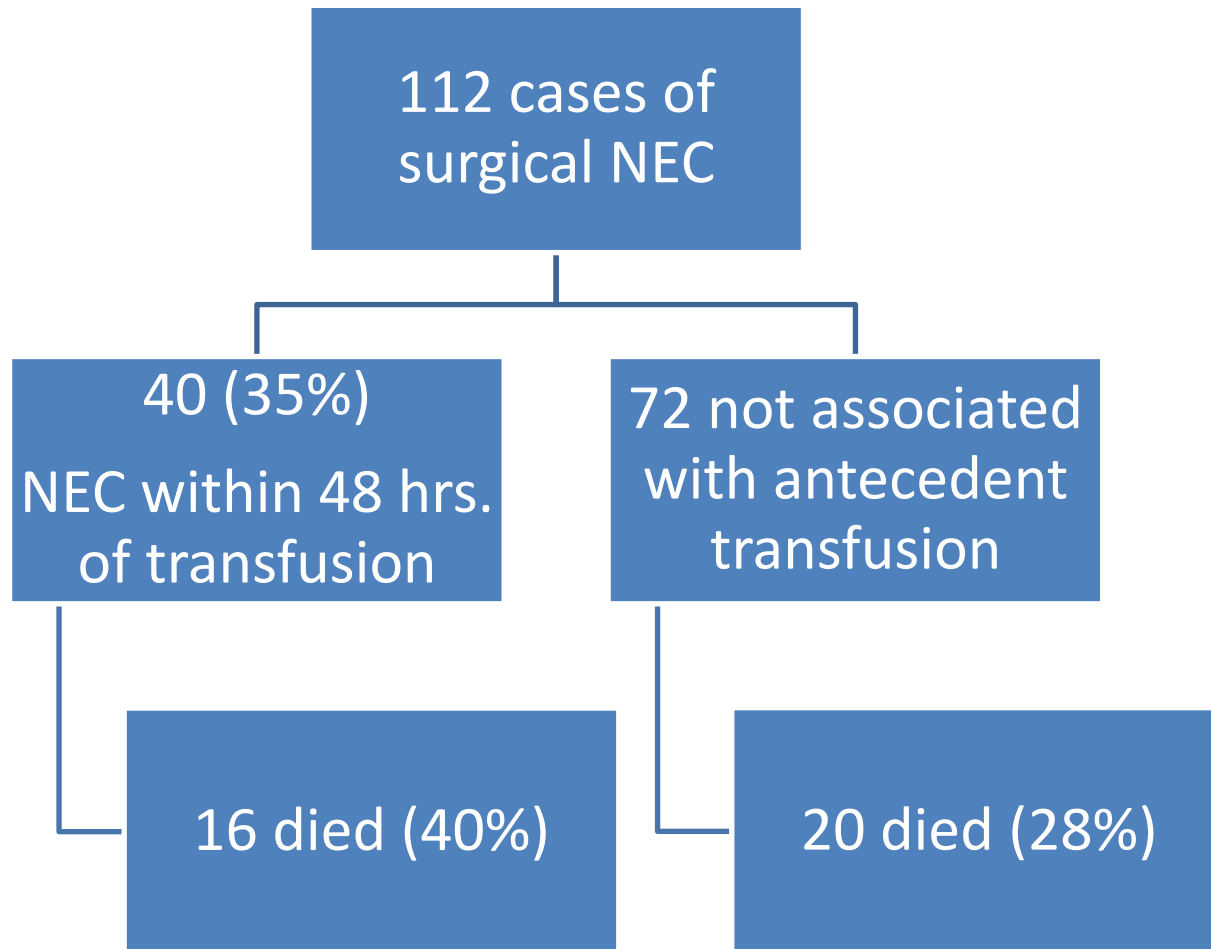
Conclusion

- In most patient RBC transfusions were temporally unrelated to NEC

- Antecedent transfusion group similar to previous studies (smaller GA, older in age, sicker)

- Late onset NEC may be a distinct entity
    - Associated with increased RBC transfusions

Another case review

Christensen et al – 2010

Results

112 cases of surgical NEC

40 (35%)
NEC within 48 hrs. of transfusion

72 not associated with antecedent transfusion

16 died (40%)

20 died (28%)

Cases of NEC vs. Controls

- NEC infants received more transfusions per infant but...
  - **50 transfusion records missing**

Oxford study

2010

Methods

- June 2006 to May 2010

- All infants born at the JR ≤ 32 wks GA

- Excluded
  - Outborn– transfusion records
  - Major congenital abnormality

- Cases identified using the computerized database and medical records

- NEC ≥ Stage 2

Results

- 494 infants identified ≤32 weeks GA born at JR

- 434 transfusions in total

- 68 cases of NEC (rate 13.5%)
  - 38 infants (55%) had an antecedent transfusion

Significant results

	Antecedent Transfusion n=38	No antecedent Transfusion n=30	
Gestation (w)	26.2 (1.9)	27.9(2.6)	<0.01
Birth weight (g)	774 (217)	1084 (406)	<0.01
Day feed started	4.2(3.5)	2.7(2.3)	0.03
Ventilation (d)	12 (3.3)	8 (2.4)	0.03
NEC stage 3 (%)	31.5	13	0.05
Death (%)	39	13	0.04

Case Control

	NEC Cases n=68	Non-NEC Controls n=140
Transfusion, n (%)	37 (55)	67 (48)
Gestation (wks), Mean (SD)	27.3 (2.8)	27.9 (2.5)
Birth weight (g), Mean (SD)	941 (383)	980 (428)

Conclusions

- NEC – do not receive more transfusions
- NEC with antecedent transfusions
  - Lower gestation
  - Lighter at birth
  - Ventilated for longer
  - More severe NEC
  - More death

Stritzke AI et al: 2012

- Retrospective study

- Canadian Neonatal Network database 2003-2008

- Cases with NEC were matched with controls by gestational age (GA) at birth (1:3)

- Transfusion associated NEC (TANEC) vs. Non transfusion associated NEC (non-TANEC) compared

NEC

	NEC cases n= 927	Non-NEC controls n= 2781
Birth weight (kg)	1.30 (0.72)	1.34 (0.74)
Transfusion exposure in previous 2 days, n (%) [c]	144 (15.5) [c]Adjusted OR: 2.44 (1.87 to 3.18)	213 (7.7)

	TANEC N=144	Non- TANEC n=783
Gestation, wks (SD) *	25.8 (2.6)	29.3 (3.9)
Birth weight, Kg (SD) *	0.885 (0.406)	1.373 (0.735)
Age at NEC, Median (IQR) *	20 (12.5–33)	14 (8–27)
SNAP II score >20, n (%) *	75 (52.1)	179 (22.9)
PDA, n (%)	98 (72.6)	249 (32.4)
Mortality, n (%)	34 (34.0)	157 (20.1)

Conclusion

- Exposure to transfusion 48hrs before a diagnosis of NEC was an independent risk factor for NEC

- Transfusion associated NEC

    - Younger
    - Lower BW

    - Higher illness severity scores.
    - No significant differences in mortality and neonatal morbidities

Meta-analysis: Mohamed et al, 2011

- 11 retrospective case-control studies
- 10 case- control studies had defined controls as 'NEC not associated with transfusion'
- Recent exposure to transfusion associated with NEC
- Neonates with TANEC
  - Younger by 1.5 weeks
  - Lower birth weight by at least 528 g
  - More likely to have PDA
  - More likely to have ventilatory support
  - Higher risk of NEC

Summary

- Retrospective

- Confounding factors (anaemia, sickness etc.) frequent

- Controls defined variably

- (very messy!)

Future

- Larger prospective studies needed to explore this entity.

- In the meanwhile
  - Withhold feeding during transfusion ?

El- Dib et al - 2011

- 6 years

- 326 infants studied

- Major difference – withheld feeds during transfusion

- NEC reduced from 5.3% to 1.3% (p=.047)

Questions

- What is the risk benefit ratio of transfusion versus anemia with respect to NEC?

- What is the best way to manage feeding during and after transfusion?

- Are there variables with blood product that we have yet to properly evaluate (for example, specific blood types, sex, race, seasonality, or preservative use)?

THANK YOU