

Gastroschisis and Omphalocele

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Anatomy and Embryology

- Imbalance between cell proliferation and apoptotic cell death
- Embryogenesis of anterior abdominal wall and umbilical cord begins at end of 3 rd wk
- Rapid growth of neuroectoderm and mesoderm transform developing embryo from disc to cylinder

Anatomy and Embryology

Gastroschisis (gestation 6-7 wk)

- Abdominal wall forms in dysplastic fashion related to decreased cell deposition or vascular abnormality (Rt. Para-umbilical vein or Rt. Omphalomesenteric artery)
- Results in thinned out area of abdominal wall right of umbilicus which ruptures due to increased abdominal pressure

Anatomy and Embryology

Omphalocele (gestation 7-12 wk)

- Abdominal cavity & enclosed organs grow at different rate
- When more space is needed by abdominal contents due to rapid growth of foregut, intestinal loops herniate into the coelomic space in the umbilical cord (physiological herniation)
- By end of 12th wk this space is obliterated
- Defective fusion of myotomes in midline/failure of closure of extracelomic space results in persistent herniation of abdominal contents

Gastroschisis

Gastroschisis

Background

- 0.3 – 2 / 10,000
- Rt. paraumbilical full thickness defect in abdominal wall
- No membrane covering bowel loops which herniate
- Chromosomes usually normal

Gastroschisis

Etiology

- Overall incidence increasing, especially in young mothers
 - W Australia Nichols et al. J Maternal Fetal Med, 1997
 - Japan (National) Sunita et al. J Pediatr Surg, 2000
 - SW England Peenman et al. Br J Obstet Gynaecol, 1998
- Young, socially disadvantaged with h/o substance abuse at highest risk (Torfs et al. Teratology, 1994)
- Association with smoking, alcohol, aspirin, and psuedoephedrine use

Gastroschisis

Etiology

- No definite teratogen identified
- Clusters of cases in communities near toxic waste sites
- Usually sporadic, but familial inheritance reported
 - a case report of mother and son
 - twins
 - siblings

Gastroschisis

Etiology

“Failure of ventral body wall closure in mouse embryos lacking a procollagen C-proteinase encoded by BMP 1, a mammalian gene related to *Drosophila* tolloid”

Sujuki et al. *Development*. 122, 3587-3595, 1996

Gastroschisis

Etiology

BMP 1 (Bone Morphogenic Protein) also called mammalian Tid

- Role in dorsal-ventral patterning of blastoderm embryo (*Drosophila*) through TGF β – related growth factor
- Mammalian & Chick BMP 1 identical to procollagenase-C proteinase that cleaves C-terminal peptide from procollagen I,II,III
- BMP 1 activates Lysyl Oxidase which is essential in forming crosslinks which stabilize fibrous forms of both collagen and elastin

Gastroschisis

Etiology

Experiment

Disrupted mouse BMP 1 gene by deleting DNA sequences encoding the active site of astacin-like protease domain

BMP 1 heterozygote mice then mated

RESULTS

Homozygous BMP-1 mutant embryos exhibit a persistent herniation of gut

Table: genotype and phenotype of embryos obtained by mating BMP 1 heterozygotes

<u>age</u>	<u>genotypes</u>		
	+/+	+/-	-/-
<i>postnatal</i>			
2 days	6	25	1*
% total	19	78	3
3 wks	45	88	0
%	34	66	0
<i>prenatal</i>			
16.5 dpc	5	15	6 **
% total	19	58	23
herniated gut	0	0	4
17.5 dpc	21	52	30***
%	20	50	30
herniated gut	0	0	25

*abd bleed, ** 1severeIUGR,no herniation, ***2dead°enerating

- Overall 24% mouse offsprings herniated gut, all genotyped as homozygous (-/-) mutant
- Homozygous mutant embryos lack membrane normally present around physiological hernia of gut
- BMP 1 is expressed in umbilical region of mid-gestation mouse embryo
- Homozygous BMP 1 mutants have defects in skull bone development but not in dorsal ventral patterning of neural tube
- **Impression: Phenotype of BMP 1 mice resembles that of human neonate with gastroschisis**

“Mutational analysis of BMP 1 gene in patients with Gastroschisis” Komuro et al. J Pediatr Surgery, 2001

Methods

Blood samples of 11 patients with Gastroschisis

Mutational analysis of exons 2-15 of the human BMP 1 gene performed using genomic PCR, single strand conformation polymorphism analogues and direct sequencing methods

Results

No mutation of human BMP 1 gene observed in any of the patients

“Mutational analysis of BMP 1 gene in patients with
Gastroschisis” Komuro et al. J Pediatr Surgery, 2001

Conclusions

Evidence of non-genetic etiology of Gastroschisis

Discussion

In homozygous null mice (-/- BMP1), 2 distinct mammalian tolloid like (mTLL) proteases designated mTLL1 and mTLL2 isolated. These are potential candidates for Gastroschisis in humans

Gastroschisis

Clinical management

- Upto 98 % diagnosed prenatally
Prenatal Ultrasound*, MSAFP (maternal alpha-fetoprotein)
- Serial ultrasound surveillance
Gastroschisis, fetal growth, meconium peritonitis (calcifications)
- Parental counseling, delivery in appropriate center
- Abdominal wall defect size – no effect on outcome
- Bowel wall thickening – adverse outcome
- Bowel dilatation – contradictory reports
- Doppler velocitometry of superior mesenteric artery- not predictor of outcome

Gastroschisis

Clinical management

Delivery

- Preterm delivery did not improve outcome
- Mode of delivery controversial for abdominal wall defects in general but especially more so for gastroschisis (than omphalocele)

Fetal abdominal wall defects and mode of delivery: a systematic review.

Segal et al. Obstet Gynecol, 98:867-73, 2001

Objective: whether there was sufficient evidence to support CS over vaginal delivery in women carrying a fetus with abdominal wall defect

Data sources: Ovid medline, review of bibliography in papers as well as in Obstetric texts

Study selection: 27 peer reviewed observational studies, 15 included in meta analysis

primary inclusion criterion: neonatal outcomes for CS vs vaginal

exclusion criterion: case series, neonatal outcomes not reported

Fetal abdominal wall defects and mode of delivery: a systematic review.

Segal et al. Obstet Gynecol, 98:867-73, 2001

Results: No significant relationship between **mode of delivery** and

- **Rate of primary facial repair** (random effects model: RR 1.22, 95% CI 0.99, 1.51)
- **Neonatal sepsis** (REM:RR 0.70, 95% CI 0.30, 1.62)
- **Pediatric mortality** (REM:RR 1.14, 95% CI 0.59, 2.21)
- **Time until enteral feeding** (RR -0.12, 95% CI -0.42, 0.16)
- **Length of hospital stay** (RR -0.16, 95% CI -0.45, 0.23)

Conclusions: No evidence of support for CS delivery for infants with abdominal wall defects

Fetal abdominal wall defects and mode of delivery

“Fetus with Gastroschisis managed by a trial of labor: ante-partum and intra-partum complications”

Anteby et al. J Perinatol, 1999

- When only bowel is herniated, a trial of labor is usually advocated, although incidence of CS may be higher (37%) than for general population
- Most agree that for very large herniations which include liver etc, CS is warranted

Associated problems and outcome

- Bowel hypomobility & feeding intolerance
 - Intestinal atresias or other bowel issues in 25% cases
 - Bowel necrosis
 - Cryptorchidism 31%
-
- Routine survival > 85%
 - Mortality from short gut syndrome / cholestatic liver disease
-
- **Long term:** 96% of available for FU (average age 16 yrs) in good health with normal growth. (Davies et al. Survivors of Gastroschisis. Arch Dis Child, 1997)

Gastroschisis: A plea for risk characterization

Malik et al. J Pediatr Surg. 2001

- **Complex:** gastroschisis with atresias, perforation, necrotic bowel, volvulus
 - **Simple:** gastroschisis only
- Does not predict which patient can undergo primary repair
- Predicts longer mechanical ventilation, length of stay and time to enteral feeds

Omphalocele a.k.a examphalos

Background

- Incidence 1-3/10,000
- Other structural abnormalities 50-70%
- Chromosomal abn. approx. 50% (frequently Trisomy13,18)
- Most common structural abn. Heart
- Associated with cloacal exstrophy, Pentology of Cantrell, neural tube defects, facial clefts

- If omphalocele contains only bowel, or associated with oligohydramnios or polyhydramnios, then chromosomal abn likely
- Sporadic, recurrence risk <1%
- Prenatal diagn: Ultrasound (>90%), MSAFP increased (89%)
- <12 wk ultrasound cannot diagnose omphalocele (physiological omphalocele)
- Pathological omphalocele can transiently reduce during an exam

- Mode of delivery less controversial
 - Aim vaginal delivery
 - Giant omphalocele can cause dystocia (CS delivery)
-
- Outcome depends on presence of associated chromosomal abn.
 - Survival >90% for isolated omphalocele

“Anuria, omphalocele and perinatal lethality in mice lacking the CD 34- related protein Podocalyxin”
Doyannas et al J Exp Med. 194, 2001

Podocalyxin

- CD 34 related sialomucin
- expressed at high levels by podocytes (glomerular epithelial cells), vascular endothelium, platelets and hematopoeitic stem cells

AIM

- To determine whether Podocalyxin plays an essential role in renal, vascular and hematopoietic function
- Authors generated a Podocalyxin deficient (podxl -/-) mice by homologous recombination

Results

Podocalyxin deficient mice (podxl -/-)

1. Perinatal lethality, omphalocele and edema
2. Neonatal anuric renal failure and death within 24 hours of birth
3. Hematopoietic and vascular endothelial cells develop normally possibly through functional compensation by other sialomucins (such as CD 34)

Perinatal lethality, omphalocele and edema (podxl -/-)

- PCR and southern blot of 6 wk old progeny from heterozygous crosses between podxl +/- revealed complete absence of any podxl -/- offspring suggesting embryonic or perinatal lethality in mice lacking Podocalyxin
- Embryo's harvested at various gestation and genotyped
- Expected mendelian frequency of podxl +/+, podxl +/- and podxl -/- observed throughout embryonic development
- All podxl -/- die within first 24 hours of life
- Birth weight of podxl +/- and podxl -/- litters similar

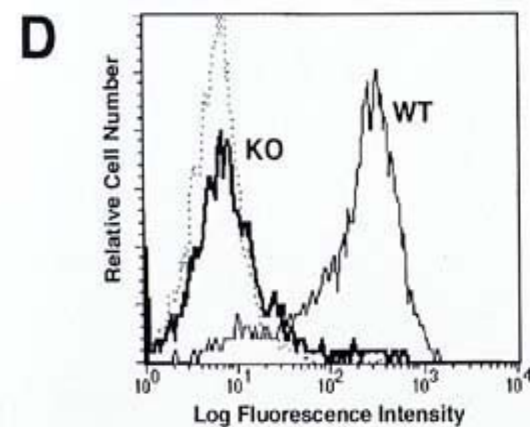
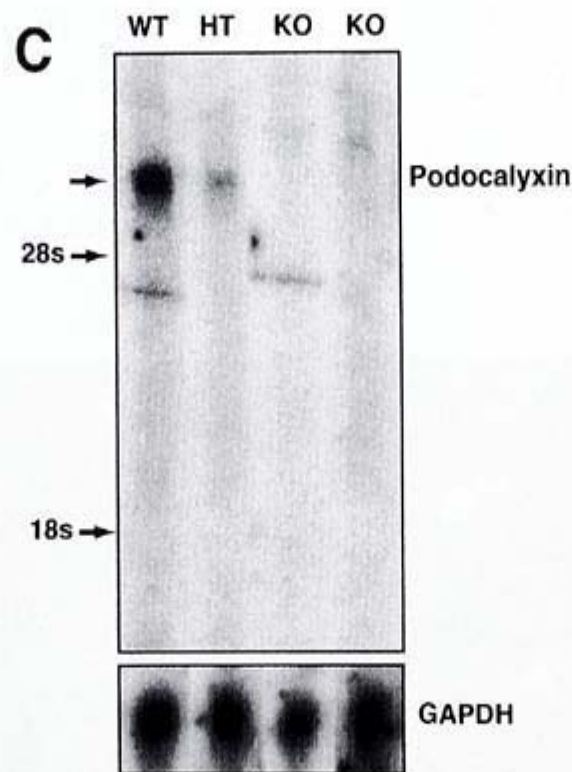
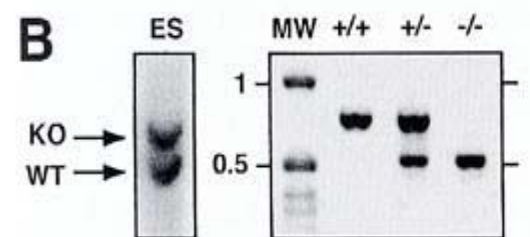
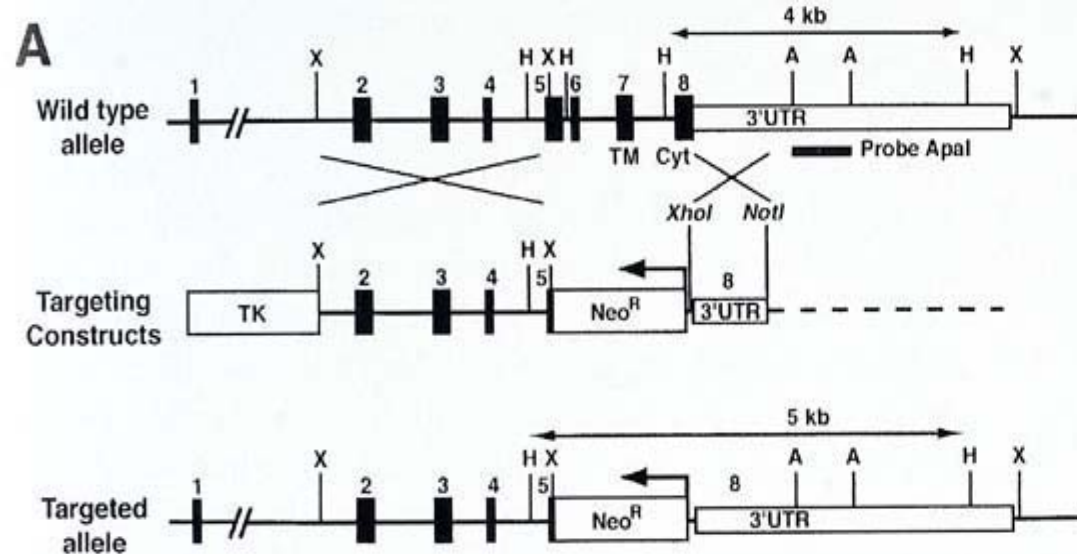


Figure 2. Generation of podocalyxin-null mutants in mice. (A) Scheme showing structure of murine podocalyxin genomic locus, targeting construct, the predicted homologous recombination event, and the targeted disruption results in the deletion of the majority of exons 5, 6, 7, and 8 encoding the 55 amino acids of the juxtamembrane ("stalk") domain, the transmembrane region (TM), and the cytoplasmic tail (Cyt). These were replaced with the neomycin resistance cassette (Neo^R) in the antisense orientation. Southern blot analysis of podocalyxin targeting in targeted ES cell clones and chimeric mice. ES clones were screened by Southern blot analysis using a podocalyxin probe, restriction sites, and predicted sizes of targeted and wild-type alleles (HindIII digest) are indicated. (B) Southern blot and PCR analysis of podocalyxin targeting in targeted ES cell clones and chimeric mice. ES clones were screened by Southern blot analysis using a podocalyxin probe to generate *podxl*^{-/-} mice. The indicated 2.2-kbp fragment was used as probe. 4-kbp wild-type (WT) and 5-kb mutant (KO) alleles are indicated. Genomic DNA from wild-type (+/+), heterozygous (+/-), and homozygous KO mice (-/-) were analyzed by PCR using allele-specific primers (see Materials and Methods). Molecular weight markers (MW) are indicated in kbp. (C) Northern blot analysis of 16-d embryo lung RNA from wild-type (WT), *podxl*^{+/-} (HT), and *podxl*^{-/-} (KO) mice. 10 μg of total RNA per lane was hybridized with probes specific to the mucin domain of podocalyxin or glyceraldehyde-3-phosphate dehydrogenase as a control. (D) Analysis of podocalyxin expression by 15-d fetal liver cells. Single cell suspensions from wild-type (WT) and *podxl*^{-/-} mice were stained with anti-PCLP-1 antibody followed by FITC-conjugated goat anti-rat antibody before flow cytometry analysis. Fetal liver cells were gated on forward and side scatter to focus on MEP21 expressing subpopulation of fetal liver.

Frequency of podxl +/+, podxl +/-, podxl -/-

<u>Age of embryos (post coitum)</u>	<u>+/+</u>	<u>+/-</u>	<u>-/-</u>	<u>frequency -/- mice %</u>
15 d	19	28	17	26%
16 d	5	21	17	27%
17 d	8	15	10	30%
18 d	35	71	30	22%
19 d	6	10	8	33%
Postpartum age				
1 d	52	100	0	0

- Perinatal lethality of podxl $-/-$ mice persists even when delivered by CS and placed with foster mother
- Majority of podxl $-/-$ mice displayed no overt defects except a subset of these mice displayed edema and omphalocele
- Approx 25% of podxl $-/-$ embryos on D 18 and D 15 exhibited mild to severe edema
- Approx 30 % of all podxl $-/-$ mice had omphalocele

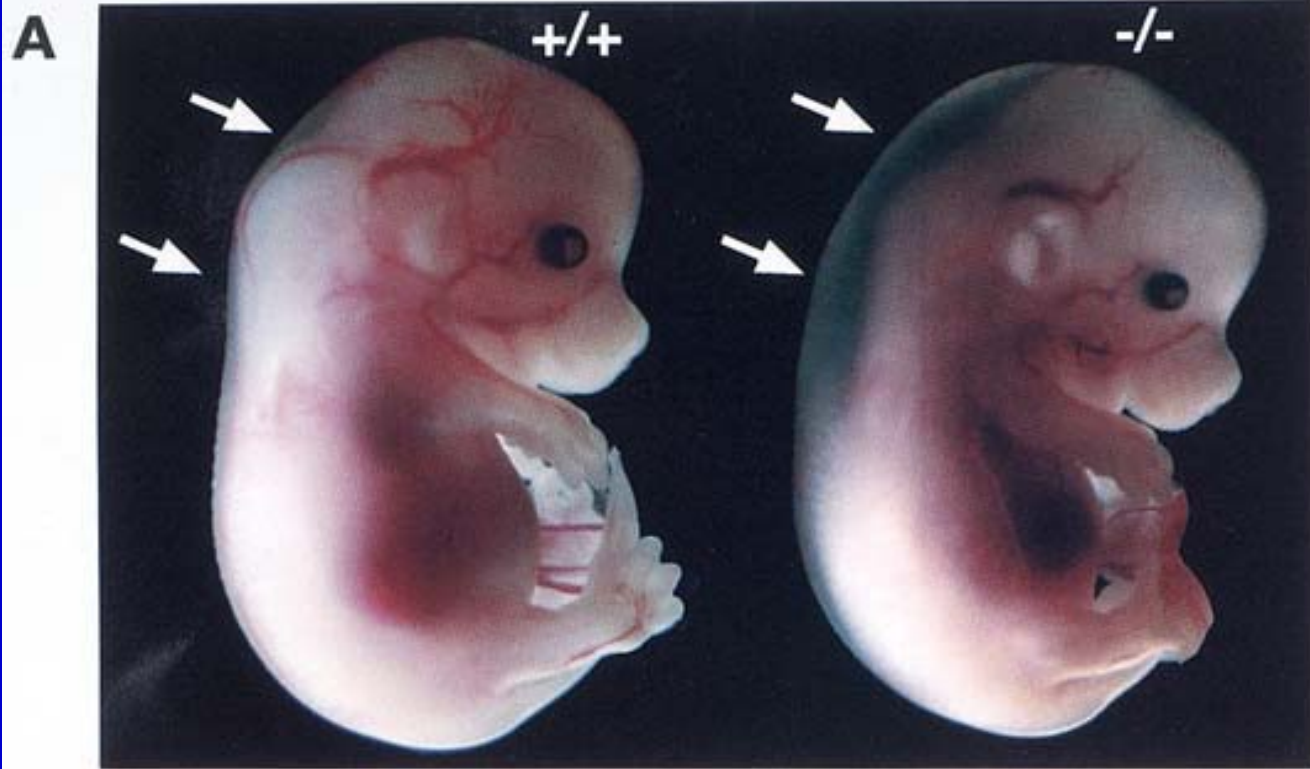
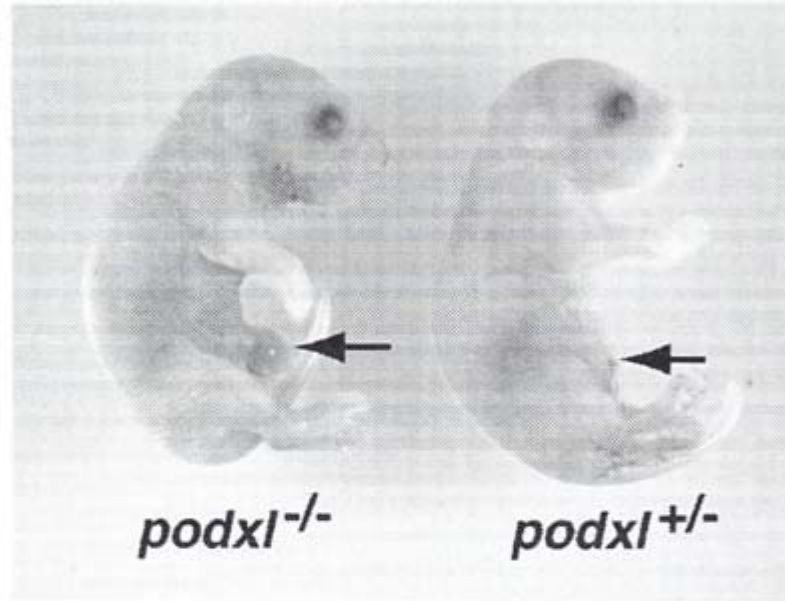


Figure 3. Edema. (A) Light micrograph of day 15 $podxl^{+/+}$ ($+/+$) embryo and one of a $podxl^{-/-}$ ($-/-$) embryo with edema. (B) Close-up color micrograph of day 15 $podxl^{-/-}$ embryo with edema. Arrows indicate the dorsal region of embryonic trunk



- $podxl^{-/-}$ mice at D18 were equally likely to have one or the other or both defects
- Neither defect observed in any D 18 $podxl^{+/+}$ or $podxl^{+/-}$
- This suggests that podocalyxin may be required for retraction of gut from umbilical cord during normal development

Role of Podocalyxin in resolution of physiological omphalocele

- In normal mouse development, gut herniates into umbilical space at embryonic day 12 and retracts back to peritoneal cavity by 16th day
- Although a subset (30%) of podocalyxin null mice displayed omphalocele at birth, all null mice showed delay in physiological omphalocele resolution in utero
- Some heterozygotes (podxl +/-) showed similar delay in omphalocele resolution suggesting a dosage effect of this mucin on resolution of omphalocele

Factors associated with outcome in gastroschisis and omphalocele

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Objectives

1. Describe the patient population treated at MHMC NICU with gastroschisis and omphalocele
2. Identify factors associated with morbidity and mortality

Methods

- Retrospective chart review (1989 to 2001)
- All gastroschisis and omphalocele patients
- Maternal and infant charts reviewed
- Data transcribed in data extraction sheet and then entered into a computer database
- Data analyzed with standard statistics software program (SPSS PC+, version 11)

Results

- A total of 59 charts identified from hospital and NICU database
- 43 had gastroschisis; 16 omphalocele
- 55/59 (gastroschisis&omphalocele) were diagnosed prenatally by ultrasound
- Of the 4 diagnosed at birth, 2 omphalocele cases born at MHMC had no PNC. Other 2 born at 2 different community hospitals had gastroschisis missed during PNC

Table 1: Patient Characteristics: Gastroschisis versus Omphalocele

	Total n=59 (%)	Gastroschisis n=43 (%)	Omphalocele n=16 (%)
Maternal age (years)	22.9±5.4	21.2±3.7	27.8±6.2*
Gravida	2.1±1.8	1.8±1.5	3.1±2.2*
Delivery (C-Section)	35(59.3%)	26(60.5%)	9 (56.2%)
Substance abuse	17(28.8%)	12(27.9%)	5 (31.3%)
Smoke	30(50.8%)	20 (46.5%)	10 (62.5%)
Gestation (weeks)	36.5±2.5	36.9±1.7	35.4±3.9
Birth Weight (g)	2443±661	2513±511	2256±953
Gender (male)	24(40.7%)	18(41.95%)	6 (37.5%)
Race			
Caucasion	38 (64.4%)	31(72.1%)	7 (43.8%)*
A Americans	16(27.1%)	9 (20.9%)	7 (43.8%)
Others	5(8.5%)	1 (7%)	2 (12.4%)
Apgar at 1 minute	6.4±2.4	6.7±2.4	5.7±2.6
Apgar at 5 minute	8.2±1.5	8.5±0.9	7.4±2.4
SNAP	11.35±5.14	11.7±4.8	10.23±6.25
Modified SNAP	17.87±6.8	18.3±6.3	16.38±8.36
Mortality	7(11.9%)	1(2.3%)	6/16 (37.5%)*

Mean ± SD

* P < 0.05

Table 2: Characteristics of infants who died

	B Weight & Gestation	Anomaly(s) Chromosomes	Repair	Age & Cause of Death
1	4.2 kg 37 weeks	Omphalocele Beckwith-Wiedemann	Primary Day 1	8 days Pseudomonas sepsis,
2	1.3 kg 32 weeks	Omphalocele Hypoplastic left heart Trisomy 18	None	2 days Trisomy 18
3	1.4 kg 26 weeks	Omphalocele Hydrops	Primary Day 1	3 days DIC, extreme prematurity,
4	1.2 36 weeks	<i>Omphalocele</i> Vater, Trisomy 18	Primary Day 1	51 days Trisomy 18
5	0.8 kg 30 weeks	Omphalocele Amniotic band syndrome Multiple anomalies	None	1 hour multiple anomalies
6	1.6 kg 36 weeks	Omphalocele Trisomy 18, multiple anomalies	None	5 days Trisomy 18
7	3.6 kg 36 weeks	Gastroschisis	Primary Day 1	10 days Liver and Bowel necrosis

- 13/16 (81.2%) omphalocele cases had variety of additional complex, major anomalies including Trisomy 18 (3/16) and Beckwith-Wideman (2/16)
- In contrast only 3/43 (6.9%) infants with gastroschisis had additional malformations (1 ASD and bladder extrophy, 1 with cleft lip and palate, amniotic band syndrome and club feet, and 3rd unilateral undescended testes)

Table 3: Characteristics of Survivors (n=52)* : Gastroschisis versus Omphalocele

	Total n=50 (%)**	Gastroschisis n=42 (%)**	Omphalocele n=8(%)*
Type of Closure			
Primary	41(82%)	34(81%)	7(78.5%)§
Secondary	9(18%)	8(19%)	1(12.5%)§
SNAP	11 \pm 4.78	11.4 \pm 4.6	8.3 \pm 5.18
Modified SNAP	17.2 \pm 5.8	17.9 \pm 5.75	13.2 \pm 5.1§
Sepsis	16(32%)	14(33.3%)	2(25%)§
NPO (days)	21.3 \pm 25.3	23 \pm 27	12.1 \pm 8.8§
Full enteral feeds (days)	28.7 \pm 25.8	30 \pm 27	20.1 \pm 17§
TPN (days)	26 \pm 25.8	28 \pm 27	15 \pm 13.2§
Ventilation (days)	7.1 \pm 7.5	6.95 \pm 6.8	7.87 \pm 11
Oxygen (days)	10.24 \pm 12.7	8.8 \pm 8	17.7 \pm 25.9
Hospital Stay (days)	36.5 \pm 28	36.7 \pm 27	35.6 \pm 34

* Medical records of 2 infants partially available (excluded from outcome analysis)

** 1 infant with short gut and outlying characteristics (excluded from outcome analysis)

§ P < 0.05

Mean \pm SD

Excluding death, patients with gastroschisis (vs omphalocele)

- appeared to be sicker
- were more likely to be septic
- needed a longer period of NPO and TPN support

Table 4: Characteristics and Outcomes: Gastroschisis by SNAP Score (n=42)*

	SNAP <10 n=15	SNAP ≥10 n=27
Maternal age (years)	21±3.7	21.5±3.8
Birth Weight (g)	2477±330	2543±598
Delivery (C-Section)	11(73.3%)	14(51.9%)
Gender (male)	6(40%)	12(44.4%)
Gestation (weeks)	37.6±1.5	36.5±1.7
Race-Caucasion	12(80%)	18(66.7%)§
Apgar at 1 minute	7.2±2.4	6.6±2
Apgar at 5 minute	8.7±1.3	8.5±0.6
Primary Closure	14(93.3%)	20(74%)§
Delivery (9-5 PM)	10(66.6%)	11(40%)
Central Line(days)	4±8.3	8.8±14.8
Sepsis	5(33.3%)	8(29.6%)§
NPO (days)	22±12.6	24.3±42§
Full enteral feeds	21±7.3	30±15§
TPN (days)	18.6±7.2	26.9±16
Ventilation (days)	4.3±3.3	8.6±7.7§
Oxygen (days)	5.9±6.3	10.5±8.5§
Hospital Stay	26.3±6.3	36.2±17§
Mortality	0	1(3.7%)§

*1 survivor with short gut with outlying characteristics (excluded from outcome analysis).

§ P < 0.05

Outcome of infants with gastroschisis

- Mode of delivery, anomaly size or the time of repair did not affect outcome of infants with gastroschisis or omphalocele
- The outcome of these patients was significantly related to their status during the first 24 hours of life as indicated by their SNAP scores.

CONCLUSIONS

- Despite a lower severity of illness score among infants with omphalocele (versus gastroschisis), more infants with omphalocele died. Those who died had lethal malformation syndromes.
- Severity of illness as indicated by a higher SNAP score adversely affects outcome of infants with gastroschisis.