The American Pediatric Surgical Association

Outcomes and Evidence Based Medicine Systematic Reviews

Treatment of Congenital Cystic Adenomatoid Malformation

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APSA Outcomes and Evidence Based Medicine Committee

Disclosures

- We have no disclosures

Systematic Review

- Attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question
- Explicit, systematic methods designed to minimize bias and provide reliable findings
- Key characteristics:
  - Clearly stated set of objectives with an explicit, reproducible methodology
  - Systematic search that attempts to identify all studies that would meet eligibility criteria
  - Assessment of the validity of the finding of the included studies
  - Systematic presentation and synthesis of the characteristics and finding of the included studies

Levels of Evidence and Grading of Recommendations

Levels of Evidence		Grades of Recommendation	
1	Systematic review of RCTs or with one RCT with narrow confidence interval	A	Consistent Level 1 studies
2	Cohort studies, low quality RCTs, outcomes research	B	Consistent Level 2 or 3 studies or extrapolation from Level 1 studies
3	Case-control studies	C	Level 4 studies or extrapolations from Level 2 or 3 studies
4	Case series	D	Level 5 evidence or inconsistent or inconclusive studies
5	Expert opinion		
	www.cebm.net RCT: randomized controlled trial		

Systematic Review Technique

- Generation of clinical questions by OEBM committee
- PubMed, WOS, Cochrane databases were searched with broad subject and MeSH headings
- Research Librarian involvement
- Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines followed
  - Public Library of Science (PLoS) Medicine 6(7):1-6
- Narrowed by reading the abstract, and then the articles
- Verified by a second author and the selections matched
- Further articles were found using the ‘snowballing’ technique

Questions posed in this systematic review

1. What is the long-term risk of an asymptomatic CCAM if observed?
2. If observation is chosen, what is the observation strategy?
3. What is the optimal operative approach (segmental / non anatomic / lobar resection) for CCAM resection?
4. What is the optimal timing for CCAM resection?
5. What is the optimal imaging modality and timing of imaging for CCAM?
6. What are the indications and outcome for fetal intervention?

Search Results

- MeSH headings searched back to 1960:
  - Cystic Adenomatoid Malformation of Lung, Congenital
  - Congenital Pulmonary Airway Malformation
    - Ultrasonography, Prenatal; Fetal diseases; Pregnancy; Hydrops Fetalis; Prenatal Diagnosis; Adult, Infant, Newborn; Bronchopulmonary Sequestration; Lung
- 1040 articles total
- All abstracts reviewed and categorized
- Cross referenced between reviewers
- 130 chosen for full review

CPAM Classification

- Stocker proposed in 1977 based on 38 cases
  - CCAM
  - Dependent on pathologic diagnosis
  - Type 1 – single or multiple large cysts (>2 cm)
  - Type 2 – multiple small cysts (<1 cm)
  - Type 3 - Large bulky noncystic lesion
  - Revised in 2002
    - Type 0, 1, 2, 3, 4 CPAM– progression down the airway (tracheal, bronchial, bronchiolar, alveolar duct and alveolar / distal acinar)

- Adzick classification
  - More clinically useful
  - Macrocystic – multiple cysts > 5 mm
  - Microcystic – more solid, cysts < 5 mm

- CVR – CCAM volume / head circumference (Crombleholme 2002)
  - To determine risk of hydrops, fetal intervention, and outcomes

A question to start . . .

- A newborn patient with a prenatal diagnosis of CPAM is born at term. They are breathing comfortably and have no oxygen requirement. CXR shows no lesion. Do you . . .
  1) Do nothing else
  2) See them back in the office in a few weeks with another CXR
  3) Obtain an immediate CT – the lesion will still be there
  4) Obtain a CT in a few weeks to months - just before resection
  5) Obtain a CT in a few weeks to months – then follow along
  6) Obtain an MRI – can't afford the radiation risk

Congenital lung malformations – an ongoing controversy.

Peters RT, Burge DM, Marven SS. Ann R Coll Surg Engl 2013 95: 144-7

- Survey of consultant members of BAPS – 51% response rate. With regard to asymptomatic lesions…
  - Imaging: 97% obtain chest xray, 91% obtain CT
  - Imaging CT timing: 50% at 6 weeks, 50% between 3-12 mo.
  - Resection: 21% always, 24% never, 55% depends (size, parental anxiety, desire for tissue diagnosis in macrocystic lesion)
  - Resection timing: 0% prior to three months, 56% prior to one year, 44% after one year
  - Follow up for surgeons who ascribe to no surgical therapy for asymptomatic lesions is highly variable

Question 1
What is the long-term risk of an asymptomatic CPAM if observed?

Question 1 - Search results

- 7 articles reviewed
- Primarily case series
- One Systematic Review / Meta-analysis of case series

Systematic review and meta-analysis of the postnatal management of congenital cystic lung lesions

Stanton et al. JPS 44:1027-1033. 2009

- Analysis of whether elective or emergency surgery associate with a higher risk of adverse outcomes
- 41 reports, 1070 patients, majority (79%) antenatally detected
- Small risk of becoming symptomatic (3.2%) if not symptomatic at birth, most by 10 months
- Two-fold increase in operative risk if operation done following symptoms
- If you're going to operate, do so before 10 months of age

Conservative management of antenatally diagnosed cystic lung malformations

Ng et al. Arch Dis Child. 99:432-437, 2014.

- 74 consecutive antenatally diagnosed patients over 10 years
- 72 live births
- 5% symptomatic
  - one emergency operation, two patients with pneumonia, one sequestration embolized
  - Three asymptomatic patients resected
- 65 asymptomatic patients, median follow up 5 years

Long-term outcome of asymptomatic patients with congenital cystic adenomatoid malformation

Wong et al. Ped Surg Int; 25:479-485, 2009.

- Series from Children's Hospital at Westmead, Sydney, Australia published in 2009
- Included patients from 1986-2007
- 35 patients identified, 21 asymptomatic at birth
- 18 patients (86%) subsequently became symptomatic at a median age of 2 years
- "Patients who present with asymptomatic CCAM will subsequently become symptomatic and warrant referral and intervention to avoid development of complications."

Will they become symptomatic?

- Some are symptomatic before birth
- Some are symptomatic at birth
- Variable whether they will be symptomatic after birth
- Probably want to operate before they are symptomatic

What is the risk of malignancy?

Pulmonary cysts in early childhood and the risk of malignancy

Priest J, Williams G, Hill D, Dehner L, Jaffe A. Pediatric Pulmonology 44:14-30, 2009.

- Review based on International Pleuropulmonary Blastoma Registry
- 220 pathology-confirmed cases of PPB (~450 total cases now)
- First described in 1988
- 66% of IPPBR cases associated with lung cysts, 29% purely cystic
- “PPB is not a pre-existing CPAM which has undergone ‘malignant transformation’”
- Sequence of low-grade PPB evolving to sarcomatous disease
- 94% present in children under 6 years old
- Inability to distinguish radiographically between CPAM and PPB

Risk factor for PPB			Degree of PPB risk
Pulmonary manifestations			
	Pneumothorax presentation		High
	Bilateral lung cysts		High
	Multifocal lung cysts		High
	Familial lung cysts		High
Associated conditions (patient or family)			
	Renal cystic disease, especially cystic nephroma		High
	Small bowel polyps		HIgh
	Additional childhood cancer or dysplasia, especially		
		Mesenchymal proliferations	High
		Gonadal tumors	High
		Any childhood cancer	High
	Nodular thyroid hyperplasia or cancer		Unknown

From Priest J, Williams G, Hill D, Dehner L, Jaffe A. Pulmonary cysts in early childhood and the risk of malignancy. Pediatric Pulmonology 44:14-30, 2009.

Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma?

Nasr et al. JPS; 45:1086-1089, 2010.

- Series from Sick Kids in Toronto, published 2010
- Included all patients with CCAM and PPB from 1999-2008
- 129 patients, 74 CCAMs resected
- 5 patients with PPB on pathology, 3 initially diagnosed with CCAM
- Incidence of 4% of PPB among apparently benign lung lesions
- No clinical or radiological markers to differentiate CCAM from PPB
- "Our experience provides further justification for resection of all CCAMs"
- Update to their prior series from 2004 which did not clearly advocate resection

Question 1 - What is the long-term risk of an asymptomatic CCAM if observed?

- 3-86% will become symptomatic
- 4% risk of pleuropulmonary blastoma
- Not clear that PPB results directly from CPAM
- Long term studies underway

(Level 4 evidence, Grade D recommendation)

Question 2
If observation is chosen, what is the observation strategy?

Question 2- Search Results

- 20 articles reviewed
- Still primarily case series
- Focus on specific follow up recommendations
- No level 1, 2, or 3 evidence available

Lack of consensus among Canadian pediatric surgeons regarding the management of congenital cystic adenomatoid malformation of the lung

Lo et al. JPS; 43:797-799, 2008.

- Survey of CAPS members in 2006 (49 surgeons)
- 69% response rate
- Variability between and even within institutions about early resection, late resection, observation
- Variation in radiographic studies, frequency, duration
- Because of the lack of literature the management approach adopted is often based on personal interpretation of the available literature

Prenatal diagnosis of congenital cystic adenomatoid malformation and its postnatal presentation, surgical indications, and natural history

van Leeuwen et al. JPS; 34:794-799, 1999.

- Study from University of Michigan
- 10 years (1988-1998) 14 patients identified and included patients diagnosed prenatally
- Four patients symptomatic at birth
- Initial uniform management
- The decision to resect a CAM in an asymptomatic patient was based on the approach of each individual pediatric surgeon

Congenital cystic adenomatoid mlaformation: monitoring the antenatal and short-term neonatal outcome

Tran et al. Australian and New Zealand Journal of Obstetrics and Gynaecology. 48:462-466, 2008.

- Important because it is from OB team rather than pediatric surgeons – different denominator – diagnosed 38 prenatal CCAM (1995-2005).
- 10% hydrops, three deaths total
- 60% of babies in whom the CCAM appeared to resolve on antenatal ultrasound had an abnormal CXR, and all their CT scans were abnormal
- Timing of CT ranged from 2 days to 4 years

Management of asymptomatic neonatal cystic adenomatoid malformations

Sauvat et al. JPS; 38:548-552, 2003.

- 10 year series, 29 patients antenatally diagnosed then asymptomatic at birth
- CCAM “vanished” in 6 patients
- 17 (59%) resected
- CT is essential for postnatal evaluation of CCAM but can be postponed until day 45 of life if asymptomatic
- If CT shows >3cm lesion or fluid, consider early surgery
- If not – follow up CT after 6-12 months

Conservative management of antenatally diagnosed cystic lung malformations

Ng et al. Arch Dis Child. 99:432-437, 2014.

- 65 patients being followed
- 5 year follow up
- Antenatally diagnosed asymptomatic patients with unilateral, single lobe lesions and no suspected genetic predisposition to malignancy
- Perform an initial CT scan at 3-6 months
- No repeated imaging in the absence of symptoms
- No indication of timing of visits

Current Expert Recommendations

Michael Stanton and Nigel Hall, Southampton Children's Hospital, UK

- Longitudinal study
- CXR at birth
- CT at 8-12 weeks
- Annual evaluation if asymptomatic
  - One lobe only
  - No family history of PPB-associated lesions
  - Cardiology evaluation if feeding vessel present

What is the observation strategy?

- At least one postnatal CT scan
- Timing of CT dependent on belief of need for and timing of resection
- May evaluate differently with increased likelihood of pneumonia, pneumothorax, family history

(Level 4 evidence, Grade D recommendation)

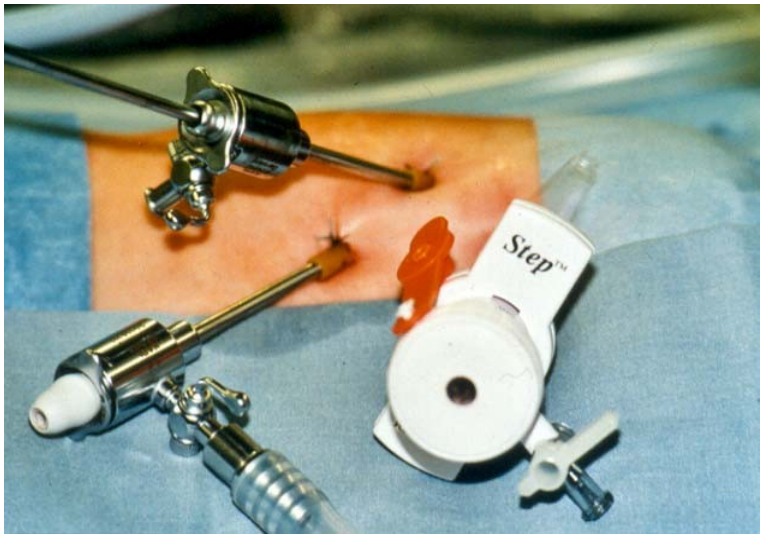
Question 3
What is the optimal operative approach (segmental / non anatomic / lobar resection) for CCAM resection?

Question 3 - Search results

- 24 studies were further reviewed where the focus was “surgical approach”
- No level 1, 2, or 3 evidence available
- Single institution retrospective studies and case reports / series

Lobectomy

- Remains the standard
- Open or thoracoscopically with excellent short and long term results
- Can we justify removing an entire lobe for a small 2 cm peripherally located lesion or a lesion that is clearly confined to a specific segment of one lobe?



Segmentectomy or Wedge Resection

- Advantages
  - Preserves parenchyma (multi-lobar disease)
  - Preserves large airway (which will not “regenerate”)
- Disadvantages
  - Missed lesions not picked up on imaging
  - Increased incidence of air leak or complications
  - Locating lesion or margins with the “naked eye” during an operation (in wedge resection)
  - Removal through small incision may distort margins which are helpful to determine adequacy of resection
  - Little long-term follow up of risk of infection/malignancy

Segmentectomy or non-anatomic resection for CCAM

Reference (1rst author)	# Patients	Notes	Follow up	Recurrence or reoperation
Browdie	3	Performed for multifocal CCAM	5 mo – 19 years	0
Fascetti-Leon	23	Complete resection defined as negative margins	Mean 65 months	0
Johnson	15	Thoracoscopic segementectomy	Mean 18 months	2/15
Kim	12	10 segmentectomy, 2 wedge	Mean 64 Months	1
Bagroda*	19	All completed thoracoscopically	Median 6 Months	0
Keiidar	3	F/U CT scan after surgery	None listed	2/3
Waszak	10	No reason for segmentectomy given	None listed	2/10
Sapin	6	Long term follow up not defined	“Long term”	1/6

* Not included in systematic review – new publication

Question 3 - What is the optimal operative approach (segmental / non anatomic / lobar resection) for CCAM resection?

- Lobectomy remains the standard of surgical resection for most CCAM
- Segmentectomy *may* be considered for *highly selected* patients:
  - Patients with multilobar disease to avoid pneumonectomy or multiple lobectomies
  - Lesion is **clearly** confined to a single segment on high quality CT or is small and peripherally located, and there is an aggressive follow-up strategy to elucidate residual disease.
  - Older patient with no potential for compensatory lung growth and lesion clearly confined to single segment on CT

(Level 4 evidence, Grade D recommendation)

Question 4
What is the optimal timing for CCAM resection?

Question 4 - Search results

- 12 studies were further reviewed with specific interest in timing of surgery – discarded singular case reports
- No level 1, 2, or 3 evidence available
- Single institution retrospective studies and case series

“Early” Resection – Hypothetical or Not?

- “Advantages”
  - Decrease in parental stress
  - Optimizes compensatory lung growth
  - Less inflammatory change may render operation easier
  - Less challenging to perform thoracoscopically
  - Those traveling to centers of excellence to deliver child may be done prior to returning home if they live in a remote location

- “Disadvantages”
  - Risks of newborn surgery/anesthesia
    - Neurocognitive Insult
    - Single lung ventilation less well tolerated
    - Higher need for postoperative mechanical ventilation

Does early resection confer fewer complications and shorter length of stay ?

Reference	Conclusion
Marshall	Early operation less complications and shorter LOS
Tsai	Short LOS and low complication rate when operation completed w/in 1rst year of life
Calvert	Early operation less inflammation at operation and histologically
Colon	No significant complications when performing surgery up to one year of age
Conforti	No difference in complication rates between early (<6 mo) and delayed (>6 mo) resection
Kim	Increasing age at resection associated with higher rate of postoperative complications
Khosa	35% developed symptoms during first year of life prior to elective resection

But, what constitutes “early”??

Thoracoscopic Lobectomy in Infants Less than 10 kg.

Rothernberg SS, Kuenzler KA, Middlesworth W, Kay S, Yoder S, Shipman K, Rodriguez R, Stolar C. J Laparoscop Adv Surg Tech 2011 21(2) 181-4.

- Retrospective review 75 lobectomies
  - 74/75 completed thoracoscopically
  - Mean age 18 weeks, Mean LOS 2.4 days, no “significant " complications.
  - Subset of 26 patients less than 3 months of age, all less then 5 kg, mean operative time 90 min, average length of stay 1.5 days. Authors noted operation “easier” technically given the lack of inflammatory change in the fissure
- Thoracoscopic lobectomy can be performed safely in infants less than 3 months.

Question 4 - What is the optimal timing for CCAM resection?

- Resection for a patient with an asymptomatic lesion is not necessary in the *immediate* neonatal period.
- However, lobectomy can be performed safely in the neonatal period and beyond equally by both open and thoracoscopic means
- Limited data would suggest that early surgery (prior to 6 months) allows for ease of operative intervention, adequate recovery, and reasonable time for compensatory lung growth

(Level 4 evidence, Grade D recommendation)

Question 5
What is the optimal imaging modality and timing of imaging for CCAM?

Question 5 - Search results

- 31 studies were further reviewed – discarded singular case reports
- 20/31 studies focused on prenatal imaging
- 3 studies CT pathologic correlation
- No level 1, 2 or 3 evidence available
- No studies comparing postnatal axial imaging technique timing, accuracy, efficacy

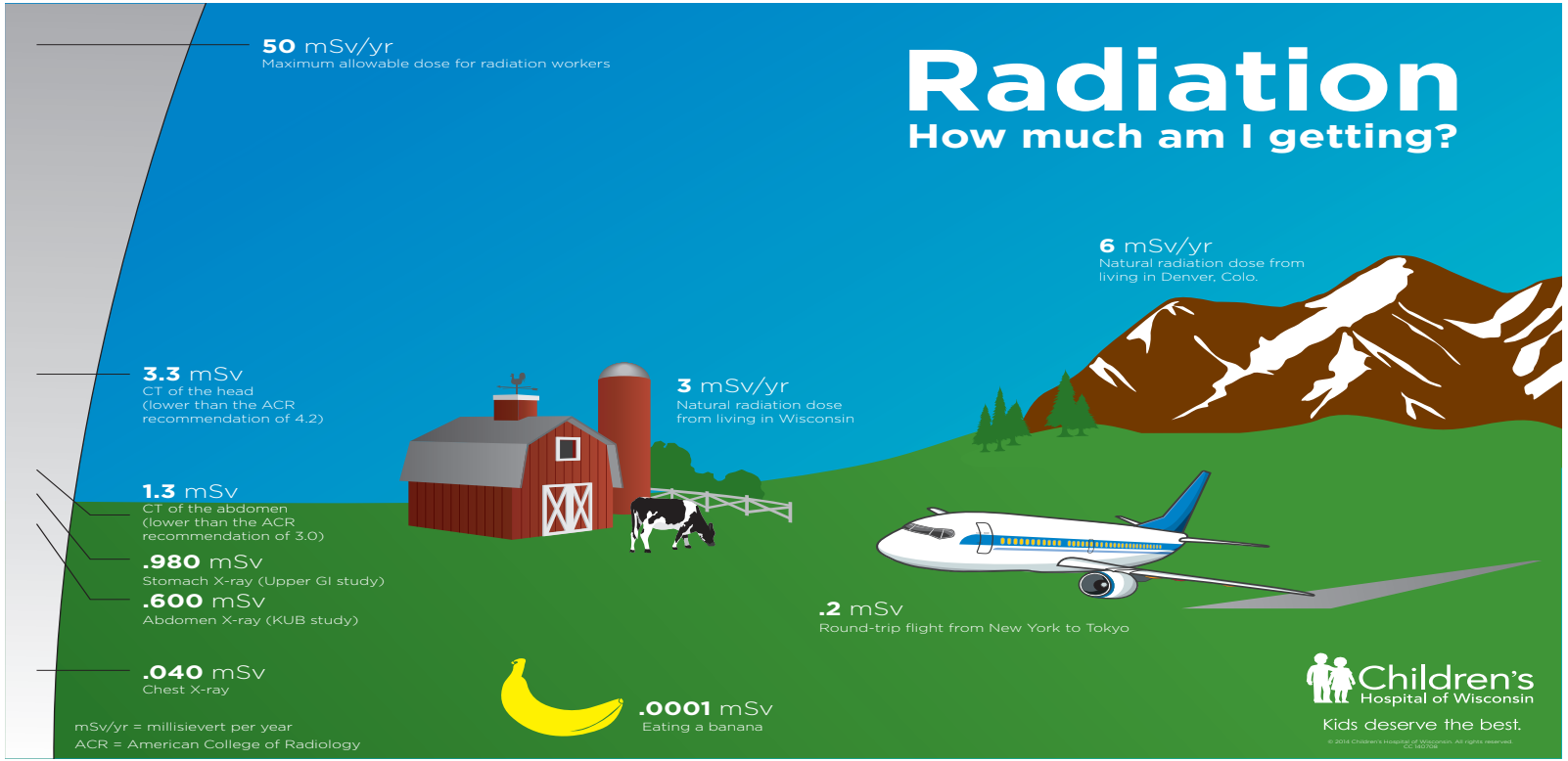
Plain film chest radiography

- Immediately following birth
  - Allows determination of mediastinal shift or large lesion that may prompt earlier intervention in an asymptomatic patient
  - If normal or lesion not visualized, then allows for re-assurance for family, however does not “rule-out” the presence of a lesion

Computerized Tomography (Multidetector CTA)

- Immediately following birth
  - Pulmonary parenchyma atelectasis may impair ability to detect multifocal disease (first week of life)
- After first 1-2 weeks of life
  - Excellent visualization of parenchyma
  - Accurately delineate multifocal disease for preoperative planning of resection
  - Allows for visualization of hybrid lesion (BPS and extra-anatomic arterial supply)
  - Superior to MRI and confers a LOW radiation dose : 2-3 millisievert

Radiation Exposure (CTA)



Question 5 - What is the optimal imaging modality and timing of imaging for CCAM for an asymptomatic patient?

- Prenatal lesions that are low risk may be followed by fetal ultrasound.
- Fetal MRI should be used in high risk lesions when fetal therapy is considered or when the diagnosis is unclear by ultrasound. There is no data to suggest that routine MRI is warranted in all cases of prenatal lung anomalies
- Plain radiography immediately after birth is useful to evaluate asymptomatic patients to evaluate findings that may prompt earlier resection
- Postnatal US – is highly operator dependent and requires an sonographic window. We *do not* recommend its routine use for surgical planning
- Multidetector Chest CT Angiography should be used in patients in whom any lesion has been noted prenatally
- Postnatal MRI is *not recommended* for routine postnatal imaging for a suspected CCAM noted on prenatal ultrasound.

Question 6
What are the indications and outcome for fetal intervention?

Question 6 - Search results

- 36 studies were further reviewed – discarded singular case reports
- No level 1,2, or 3 evidence available
- Particular attention paid to prenatal indications for intervention and/or treatment

High Risk CCAM

Potential Benefit for Fetal Treatment

- CVR > 1.6 (risk of hydrops >75%)
  - CVR = CCAM Volume/Head Circumference
    - CCAM volume = length x height x width x 0.52)
  - CVR <1.6 in absence of dominant cyst risk of hydrops less than 3%
- Hydrops – early vs standard
- Placentomegaly
- Echocardiographic changes
- Diaphragm Eversion
- Severe Mediastinal Shift
- Lung volume deficiency (MRI)
- Maternal Mirror Syndrome

Modalities – CCAM Fetal Treatment

- Maternal Steroids
- Serial cyst aspiration
- Thoracoamnionic shunt
- Percutaneous Laser Ablation
- Percutaneous Sclerotherapy
- Fetal Lobectomy/Resection
- EXIT to Lobectomy/Resection

Prenatal Steroids for High Risk CCAM

Reference (1rst author)	# Patients	Center	Characteristics	Hydrops (Resolution)	Survival to discharge
Curran 2010 Loh 2012 Tsao 2003	13	UCSF	All microcystic	9 with hydrops (7 resolved)	11/13 (85%)
Morris 2009	15	Cincy	7 Macrocystic 8 Microcystic	Macrocystic 7 hydrops (2 resolved) Microcystic 6 hydrops (5 resolved)	Macrocystic 2/7 (29%) Microcystic 6/8 (75%)
Pertanteau 2007	11	CHOP	All microcystic	5 with hydrops (4 resolved)	100%

Prenatal betamethasone is effective for the fetus with a microcystic lesion with a high risk fetal profile and should be highly considered

Thoracoamnionic Shunting for Fetal CCAM
Combined Results from 28 reports

# Cases		Survival	
With hyrdops	No hydrops	With hydrops	No hydrops
54	35	67%	94%

- Feasible
- Improves survival in patients with hydrops or in patients at risk of developing it.
- More durable than serial thoracentesis.

Question 6 - What are the indications and outcome for fetal intervention?

- Prenatal steroids should be administered to mothers carrying a fetus with a microcystic CCAM with “high risk” factors.
- Thoracoamnionic shunting should be offered when a fetus has a macrocystic lesion (a dominant macrocyst) with “high risk” factors.
- Consultation with a center with fetal treatment expertise should be highly considered in cases of high risk CCAM noted prior to birth, especially when thoracoamnionic shunting or open fetal resection, or EXIT to resection modalities may be of potential benefit.

(Level 4 evidence, Grade D recommendation)