Hypertension and Renal Disease in Pregnancy

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Hypertension:
The most common medical complication of pregnancy

- ~15% of first pregnancies
- ~5% of subsequent pregnancies

Relative frequencies of hypertension in pregnancy

Pregnancy and hypertension

- 26 year old primigravid in good health
- 24/52 BP 118/72
- 28/52 BP 142/95; no proteinuria

Baby well-grown and active

? Diagnosis  ? Action

Gestational hypertension

- Development of isolated hypertension during antenatal period, after 20 weeks and resolving within 6 weeks postpartum
- BP > 140/90 mmHg seated
- ~20% of these women develop other features of pre-eclampsia
- Related to gestation at presentation
- Gestational hypertension tends to recur with each pregnancy

Treatment

- Screen for secondary causes
- Surveillance for preeclampsia
- Treatment of hypertension
- Above a MAP of 150 there is a loss of cerebral autoregulation and risk of stroke
- Foetal surveillance
- Decision regarding timing of delivery
30 weeks

Preeclampsia: predisposing factors
- Genetic predisposition
- Nulliparity
- Multiple gestation
- Previous preeclampsia
- Obesity
- Maternal thrombophilia
- Maternal vascular disease
  - renal disease
  - diabetes mellitus
  - chronic hypertension

Multi-organ features
- Hypertension and proteinuria
- Renal dysfunction
- Activation of coagulation
- Hepatic dysfunction
- CNS dysfunction
- CVS dysfunction
- Fluid balance
- Placental dysfunction

Pre-eclampsia

Prevention
Control risk factors
- Diabetes
- Aspirin for high risk patients

Management
- Empirical
- Temporisation - foetal welfare
- Resolution after delivery

Oral antihypertensives & close monitoring of severe pre-eclampsia - better outcome than immediate delivery

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Delivery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (24-27/52)</td>
<td>54</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Prolong’n</td>
<td>13d</td>
<td>2d</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B.Wt (g)</td>
<td>880±212</td>
<td>709±159</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PNM</td>
<td>13 (24%)</td>
<td>20 (65%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(Sibai et al 1990)</td>
<td></td>
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</tr>
<tr>
<td>N (28-34/52)</td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Prolong’n</td>
<td>7d</td>
<td>1d</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>B.Wt (g)</td>
<td>1420±350</td>
<td>1272±357</td>
<td>NS</td>
</tr>
<tr>
<td>NN morbidity</td>
<td>6 (30%)</td>
<td>15 (83%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>(Odendaal et al 1990)</td>
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</tr>
</tbody>
</table>
**32 weeks**

- **BP 138/82**
- **u protein 0.7g/d**
- Estimated interval foetal growth 220g
- CTG reactive

? Action

**33 weeks**

- **BP 150/100**
- **u protein 1.1g/d**
- **LFTs normal, platelet count normal, SUA 0.4mmol/L**
- Foetus active, biophysical profile and CTG satisfactory

? Action

**34 weeks**

- **BP 175/115**
- **protein 2.1g**
- **SUA 0.5**
- **plt 90000**
- **AST 65**
- **ALT 70**
- **CTG non-reactive, but no decels**

? Action

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**Chronic Hypertension**

- Superimposed preeclampsia
- 2 fold for those requiring medication
- 46% if DBP> 110 before 20 weeks
- Particular risk of early onset pre-eclampsia
- IUGR
- Placental abruption

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**Chronic hypertension has a deleterious effect on pregnancy**

- Close relationship between perinatal survival and severity of chronic hypertension
- Proteinuria develops frequently in women with initial systolic BP>140 mmHg
  
(Browne, Dodds 1942 Chasley, Annitto 1947)
Control of chronic hypertension results in fewer episodes of exacerbation in later pregnancy.

Control of chronic hypertension results in a lower incidence of perinatal mortality in later pregnancy.

Antihypertensive drugs used in pregnancy:
- Centrally acting drugs (methyl DOPA, clonidine)
- Beta blockers (propranolol, oxprenolol, metoprolol, pindolol, atenolol, labetalol)
- Calcium channel blockers (nifedipine SR, verapamil)
- Vasodilators (hydralazine, diazoxide)
- NO donors (sodium nitroprusside, isosorbide mononitrate, glyceryl trinitrate)
- ACE inhibitors, AII antagonists
- Diuretics

Principles of management of hypertension in pregnancy:
- Treat blood pressure persistently above 140/90 mmHg (sitting, phase V diastolic)
- Use agent suitable for pregnancy
- Aim for blood pressure ~130/80 mmHg
- Aim for vaginal delivery close to term if possible
- Supervise maternal and foetal welfare closely
  - Renal, hepatic, coagulation status
  - Fluid balance
  - Foetal growth, activity, cardiac reactivity

Pre-existing renal disease and pregnancy

Pre-pregnancy factors of importance:
- Urinary tract infection
- Renal function
- Blood pressure
- Nature of renal disease
Urinary tract infection and pregnancy

**Risk factors for pyelonephritis**
- Asymptomatic bacteriuria (6-8% prevalence)
- 40% develop symptomatic UTI
- 30% develop acute pyelonephritis if untreated
- Anatomic changes of the urinary tract
- Diabetes, steroid therapy, recurrent UTI

**Effects of pyelonephritis**
- Dehydration
- Impaired glomerular function
- Premature labour and low birth weight babies

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**Pregnancy and renal disease**

<table>
<thead>
<tr>
<th></th>
<th>MILD Cr&lt;125</th>
<th>MOD Cr&lt;170</th>
<th>SEVERE Cr&gt;170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>20-25%</td>
<td>40-50%</td>
<td>80-90%</td>
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<tr>
<td>Successful outcome</td>
<td>90-100%</td>
<td>80-90%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Long term problems</td>
<td>2-4%</td>
<td>20-30%</td>
<td>50-60%</td>
</tr>
</tbody>
</table>

**Pregnancy and renal function**

<table>
<thead>
<tr>
<th></th>
<th>MILD Cr&lt;125</th>
<th>MOD Cr&lt;170</th>
<th>SEVERE Cr&lt;220</th>
<th>BAD Cr&gt;220</th>
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<tbody>
<tr>
<td>Loss of function</td>
<td>2%</td>
<td>40%</td>
<td>65%</td>
<td>75%</td>
</tr>
<tr>
<td>Post part deterioration</td>
<td>20%</td>
<td>50%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>ESRF</td>
<td>2%</td>
<td>33%</td>
<td>40%</td>
<td></td>
</tr>
</tbody>
</table>

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**Pre-pregnancy renal function and progression**

- Impaired pre-pregnancy renal function is associated with an increased risk of further deterioration during pregnancy.
- This deterioration may be permanent and termination of pregnancy is unlikely to restore renal function in those with severe renal failure

- Hypertension is associated with a greater risk of deterioration of renal function in late pregnancy
- Hypertension is not associated with permanent deterioration of renal function post-partum

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**CRF & Pregnancy**

- Pre-eclampsia
- IUGR
- Preterm delivery
- Increased perinatal mortality
- Outcome better with good BP control and better renal function

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Renal disease and pregnancy

- An increase in the degree of proteinuria is very common in pregnancy
- Treatment with low dose aspirin should be considered in view of increased risk of preeclampsia

Pregnancy in dialysis patients and following renal transplantation

Dialysis - maternal complications

- Low fertility: 1/200 women per year
- Accelerated hypertension (~10%)
- Underlying disease problems (eg SLE)
- Poor prognostic factors:
  - Age>35 years
  - More than 5 years on dialysis
  - Delayed diagnosis of pregnancy

Dialysis - perinatal complications

- Polyhydramnios
- Prematurity (median gest. age 32.4 weeks)
- Fetal growth restriction (28% SGA - <10th centile)
- Congenital abnormalities (11/49 =22%)
  (Tetralogy of Fallot, dev. delay, blindness)
- 30% chance of successful outcome

Dialysis and pregnancy outcome

(EDTA 1980, 1986; Rose (USA) 1985; Souqiyeh (S Ar) 1992; Hou (USA) 1994; Okundaye (USA) 1994; Giatras 1998)

ANZDATA

1992-2002
- 1368 women of child bearing age on dialysis
- 15 pregnancies in 14 women on dialysis
- 4 live births
Pregnancy and dialysis management

**Pre-conception**
- Counselling
- Contraception
- BP control

**Pregnancy**
- Increase dialysis
- Increase EPO
- Increase heparin
- Reduce Ca/vit D

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Pregnancy and renal transplantation

**29 year old lady G1P0 8 weeks pregnant**
- ESRF due to reflux nephropathy
- 2 years on HD
- 10 years ago living related transplant from her mother in Sri Lanka
- Stable function with Cr 95 (GFR 61ml/min)
- Stable immunosuppressive requirements
- BP 140/90 on most clinic visits

**Concerns**
- ? Action

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Pregnancy and renal transplantation

**Medications**
- Atenolol 50mg daily
- Cardizem 180mg daily
- Cyclosporin 25mg BD
- Prednisone 5mg daily
- Azathioprine 50mg daily

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Graft function is not usually adversely affected by intercurrent pregnancy when Cr<0.10
- Cr>130 renal graft survival only 65% at 3 years

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Renal transplantation and pregnancy

- Successful outcome beyond 12 weeks:
  - 97% with Cr<125
  - 75% with Cr>125
- 50% have some foetal problem:
  - IUGR
  - Preterm delivery

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Pregnancy post-transplantation

**Pre-conception**
- Counselling
- Stable renal function : ideally 2 years
- Good BP control
- No proteinuria
- Drugs altered as much as possible
- Consider increased risk of Preeclampsia and UTI

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Sturgiss 1992; First1995; Armenti 1995; Hou 1999; Salmela 1993
Summary - renal disease and pregnancy

- Childbearing should be regarded as one of the goals of treatment for renal disease in women of childbearing age, rather than as an accident to be dealt with when it occurs.
- Care of the pregnant woman with renal disease should be supervised by an experienced multidisciplinary team.
- The aim should be to ensure the safety of the mother and to maximise the chances of survival and normal development for the infant.

Pregnancy and hypertension

- 31 year old primigravid in good health.
- Booking BP 90/62.
- 28/52 diet controlled gestational diabetes.
- 36/52 Headaches, spots in her visual field, epigastric pain.

36 weeks

- BP 145/80.
- No oedema.
- Normal fundoscopy.
- Normal reflexes/no clonus.
- No epigastric tenderness.
- U protein/cr 81.
- Urate 0.28.
- Plt 264.
- LFT normal.
- Cr 65.
- Foetus active, biophysical profile and CTG satisfactory.

Management

- Patient admitted.
- Expectant management with no anti-hypertensive introduction.

Over the next five days

- The symptoms persisted.
- BP was labile but never went above 150/100.
- She was commenced on oxprenolol 40 mg tds which maintained her BP below 140/90.
- Neurological examination remained normal.
Eclampsia

- Day 5 tonic clonic seizure after ROM
- Managed with Mg So4
- CTG non-reassuring 5 minutes after seizure
- Emergency LSCS

Investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Plt</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td>0.28</td>
<td>0.35</td>
</tr>
<tr>
<td>Alb</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Prot/Cr ratio</td>
<td>81</td>
<td>370</td>
</tr>
</tbody>
</table>

What is eclampsia?

- Convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of preeclampsia

- 4-5 cases per 10,000 live births in developed countries

Can we predict it?

Diagnosis

- Oedema
- Hypertension
- Proteinuria
- Symptoms
### Diagnosis

<table>
<thead>
<tr>
<th>Oedema</th>
<th>Absent 26%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Absent 16%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Absent 14%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Absent 25%</td>
</tr>
</tbody>
</table>

### Diagnosis

<table>
<thead>
<tr>
<th>Oedema</th>
<th>Absent 26%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>&gt;160/110 20-54%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&lt;160/110 30-60%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≥ 3+ 48%</td>
</tr>
</tbody>
</table>

### Can we predict it?

- 20 to 40% max BP < 140/90
- 20% no proteinuria
- Eclampsia may be the first manifestation of pregnancy related hypertensive disease both pre and post partum

### Can we prevent it?

#### Primary prevention

- Low risk patients
  - 15 RCT antihypertensives
  - 2 RCT magnesium
  - 2 RCT zinc
  - 3 RCT fish oil
  - 7 RCT calcium supplementation
  - Minimal to no benefit

#### Tertiary

- Secondary
Aspirin for primary prevention

2 multicentre RCTs in nulliparous women
- 3000 women 60mg aspirin v placebo at 13-26 week (Sibai et al NEJM 1993)
  - Slight reduction in incidence of preeclampsia: not sig
  - No differences in birth weight or IUGR incidence
- 3294 women 100mg aspirin v placebo from 14-20 wks until 36 wks (Subtil et al BJOG 2003)
  - PE incidence low and similar in both groups
  - No difference in foetal growth restriction

Aspirin for primary prevention

3 large RCTs in moderate to high risk women
- Over 13000 women in total
- A small decrease in the incidence of preeclampsia in each trial, but not statistically significant:
  - 15 v 19%; 18 v 20%; 6.7 v 7.6%
- CLASP study showed a shift towards later development of preeclampsia with aspirin treatment

Aspirin for primary prevention

2 Meta analyses
- Coomarasamy et al Obs Gyn 2003
  - 14 trials with over 12000 women at risk
  - Aspirin reduced the risk of preeclampsia, perinatal death, preterm birth but did not alter birth weight or abruption
- Askie et al The Lancet 2007
  - 31 trials with 32,217 women and their 32,819 babies includes nulliparous women
  - Aspirin reduced the risk of preeclampsia, delivering before 34 weeks, or having a pregnancy with serious adverse outcome (RR0.9 and no diff in diff groups)
  - No sig effects on IUGR, risk of death for foetus or baby

Can we prevent it?

Primary  5-10% pregnancies develop preeclampsia
Secondary 0.5% mild and 2-3% severe preeclampsia develop eclampsia

Secondary prevention

Early detection of gestational HT or preeclampsia and subsequent prevention
- Close monitoring
- Anti hypertensive therapy
- Prophylactic use of magnesium sulphate

Secondary prevention

Early detection of gestational HT or preeclampsia and subsequent prevention
- Close monitoring
  - No RCT
  - Retrospective studies in developed countries show that around 50% of eclamptic women develop their first seizure in hospital under close supervision
Secondary prevention

- Early detection of gestational HT or preeclampsia and subsequent prevention
- Close monitoring
- Antihypertensive therapy
- Several RCT that are not powered to detect a change in incidence of eclampsia
- Trials tend to show a lower rate of progression of Gestational HT or preeclampsia to more severe disease

Prophylactic use MGSO4

- 4 RCTs MGSO4 v placebo or no tx (± anti-HT)
- Overall significantly lower rate of eclampsia in severe preeclampsia (0.6% v 2%)
- No significant benefit in either maternal or perinatal outcomes

Mild preeclampsia

- 2 RCT in mild preeclampsia
- Small numbers
- No eclampsia and no difference in rate of progression to severe preeclampsia

Secondary prevention

- Early detection of gestational HT or preeclampsia and subsequent prevention
- Close monitoring
- Antihypertensive therapy
- Prophylactic use of magnesium sulphate

Prophylactic use MGSO4

- MAGPIE trial
- 10,000 women with preeclampsia (75% mild and 25% severe)
- With “imminent eclampsia” NNT 36
- Without symptoms NNT 129
- Developed countries NNT 385
- Trend towards a reduced rate of maternal death
- Maternal morbidity, perinatal mortality and neonatal morbidity was similar in both groups

Mild preeclampsia

- Large observational series (72000 pts):
  - MgSO4 was given to pts with severe pre-eclampsia but not to mild, as previously
  - Severe preeclampsia:
    - >140/90 plus 2+ proteinuria or Cr >106 or AST x2 or plt<100 or clinical symptoms
    - 0.12% developed eclampsia representing an increase in 50% on historical controls

**Down sides**

- Mild side effects in 15-67% of patients
- Major side effects: respiratory depression and postpartum haemorrhage (2.4% vs 1%)

**Series of systematic reviews reported that**

<table>
<thead>
<tr>
<th>Study</th>
<th>Magnesium (mg)</th>
<th>Control (mg)</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duley et al</td>
<td>4 (14,52)</td>
<td>0 (7,1)</td>
<td>2.08 (0.92-4.85)</td>
</tr>
<tr>
<td>Maclean et al</td>
<td>6 (19,51)</td>
<td>0 (7,1)</td>
<td>0.02 (0.01-0.20)</td>
</tr>
<tr>
<td>Total</td>
<td>4 (14,52)</td>
<td>0 (7,1)</td>
<td>1.08 (0.32-3.45)</td>
</tr>
</tbody>
</table>

- Effects only on seizure: no effects on progression of other aspects of preeclampsia

**Tertiary prevention**

- 2 RCTs by Eclampsia Trial Collaborative Group comparing magnesium sulphate to diazepam or phenytoin for prevention of further seizures.
  - MgSO4 reduces risk of recurrence by 1/3 to 2/3
  - MgSO4 reduces risk of maternal death by 1/3
- Series of systematic reviews reported that MgSO4 was safer and more effective than phenytoin, diazepam or a cocktail

**Can we prevent it?**

Primary 5-10% pregnancies develop preeclampsia

Secondary 0.5% mild and 2.3% severe preeclampsia develop eclampsia

Tertiary 5-25% eclamptic patients have recurrent seizures

**Can we prevent it?**

Primary Aspirin for high risk women

Secondary Perhaps MgSO4 for severe preeclampsia

Tertiary MgSO4 to prevent recurrent seizures

**Can we prevent it?**

- The low incidence of eclampsia in developed countries probably relates to prevention of classic cases
- Most eclamptic convulsions in reported series have atypical presentation
- The percentage of eclampsia considered unpreventable in these series range from 31 to 87%

**Eclampsia**

- 40 year old primigravid in good health
- Booking BP 112/86
- 25/52 BP 175/92
  - 4+ proteinuria
  - Baby well-grown and active
Eclampsia

40 yr old
G2P0
25+1/40 admitted to another hospital because of BP of 170-180/90 and the presence of 4+ protein in the urine
On arrival she c/o constant headache for the past 2-3 days without any visual symptoms and her BP on arrival was 227/126 (both manual and automatic sphygmomanometer)

Management

- Attempts made to control BP
- 3 hours after admission, she had a tonic clonic seizure
- She was resuscitated with IV Diazepam and Magnesium with subsequent transfer to ICU

Treatment

- Oxygen during seizure
- MgSO4 to treat and prevent recurrence
  - Loading dose plus maintenance dose (24 hrs after del and/or last convulsion)
  - 10% of women will have a further seizure and further bolus can be given
- Control hypertension to BP 140/90 to 160/110
- Foetal heart changes usually resolve within 10 minutes
- Not necessarily an indication for Cesarean section

25 weeks

- Hb 132
- Plt 239
- Cr 51
- Urate
- Alb 24
- LFT normal
- Prot/Cr ratio 3548
- Foetus active; biophysical profile and CTG satisfactory

Impact on mother

- Increased maternal death rate (0-1.8%) but 14% in developing countries
- Risk of death higher for women older than 30, no prenatal care and pregnancies at or before 28 weeks
- Maternal complications are relatively common as with preeclampsia

How to treat it?

- What is its impact on mother and baby?
- What are the risks for subsequent pregnancies?
**Stroke and PE/Eclampsia**

- Accounts for 35-45% deaths from PE/Eclampsia
- Complicates 1-3% cases eclampsia and 0.1-0.5% cases PE

**Impact on baby**

- Recent series reported perinatal death rate at 5.6 to 11.8%
- Related to prematurity, abruptio placentae and severe foetal growth restriction

**Risk for future pregnancies**

- Eclampsia occurs in 2% of future pregnancies
- Also at increased risk of preeclampsia and other obstetric complications (abruptio placentae, preterm delivery, IUGR and perinatal mortality)
- Risk amplified if Preeclampsia/Eclampsia developed less than 28 weeks gestation

**Subsequent pregnancies**

Study followed 159 nulliparous women with a history of eclampsia and no pre-existing HT through 334 subsequent pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Mild PE</th>
<th>Severe PE</th>
<th>Eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>13%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Eclampsia</strong></td>
<td>17%</td>
<td>25%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>&lt;30 weeks</strong></td>
<td>17%</td>
<td>25%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Martin et al. Obstet Gynecol Feb 2005**
**What is eclampsia?**

- Pathogenesis of cerebral pathology unknown
- CT and MRI: oedema and infarction within subcortical white matter and adjacent grey matter in around 50%
- Cerebral angiography: vasospasm
- ?Hypertensive encephalopathy

**What is PRES?**

- Headache/visual symptoms/confusion/seizures combined with classic neuroimaging changes
  - Symmetrical white matter oedema in the posterior regions of the brain
- Hypertensive encephalopathy
- Eclampsia
- Immunosuppressive agents