

Preventing neonatal fungal infections

David Isaacs

**Children's Hospital at Westmead
University of Sydney, Australia**









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Tel: +41 22 906 0488; Fax: +41 22 906 9140; E-mail: wspid@kenes.com
Web: www.kenes.com/wspid

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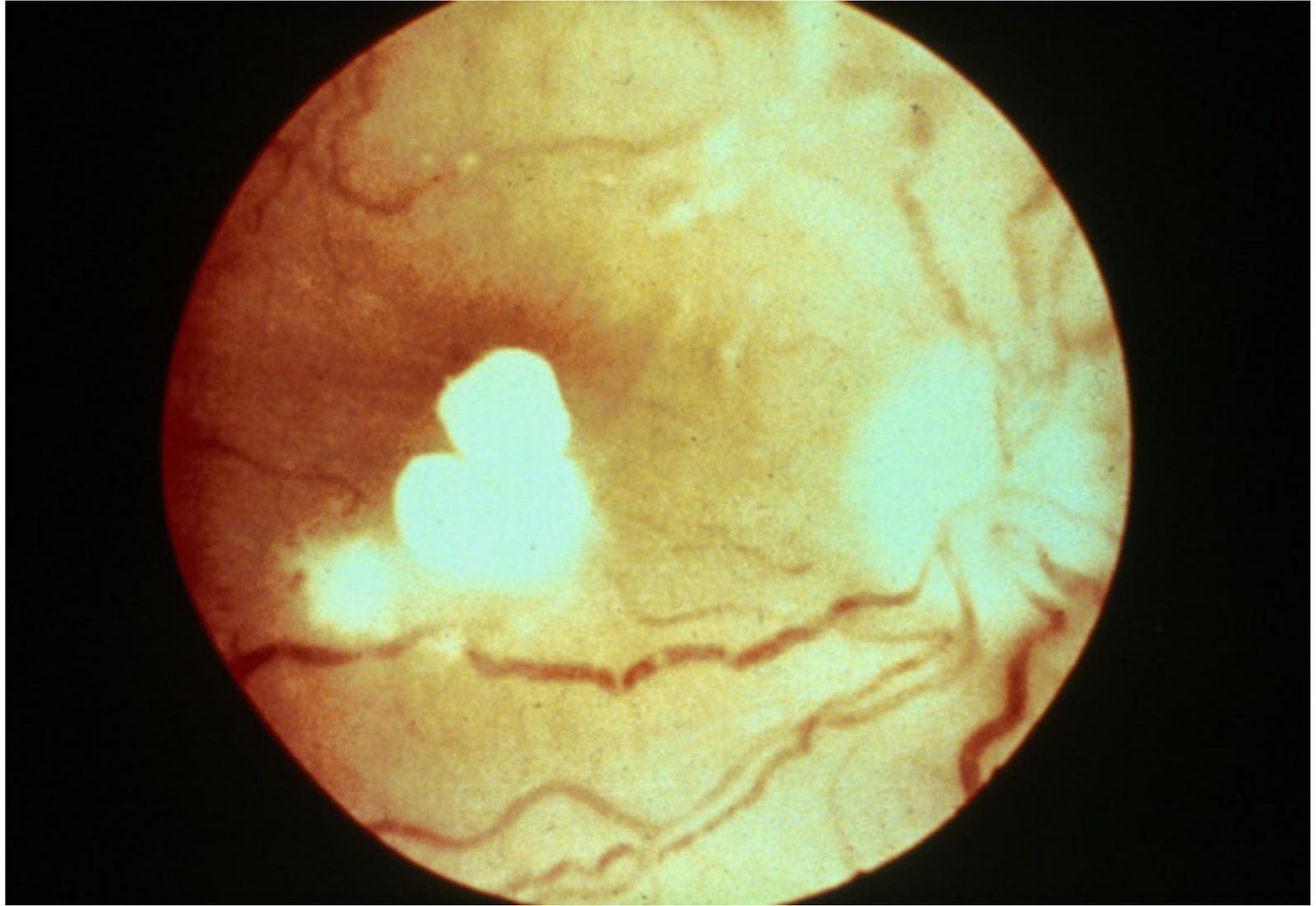
Invasive fungal infection in neonates

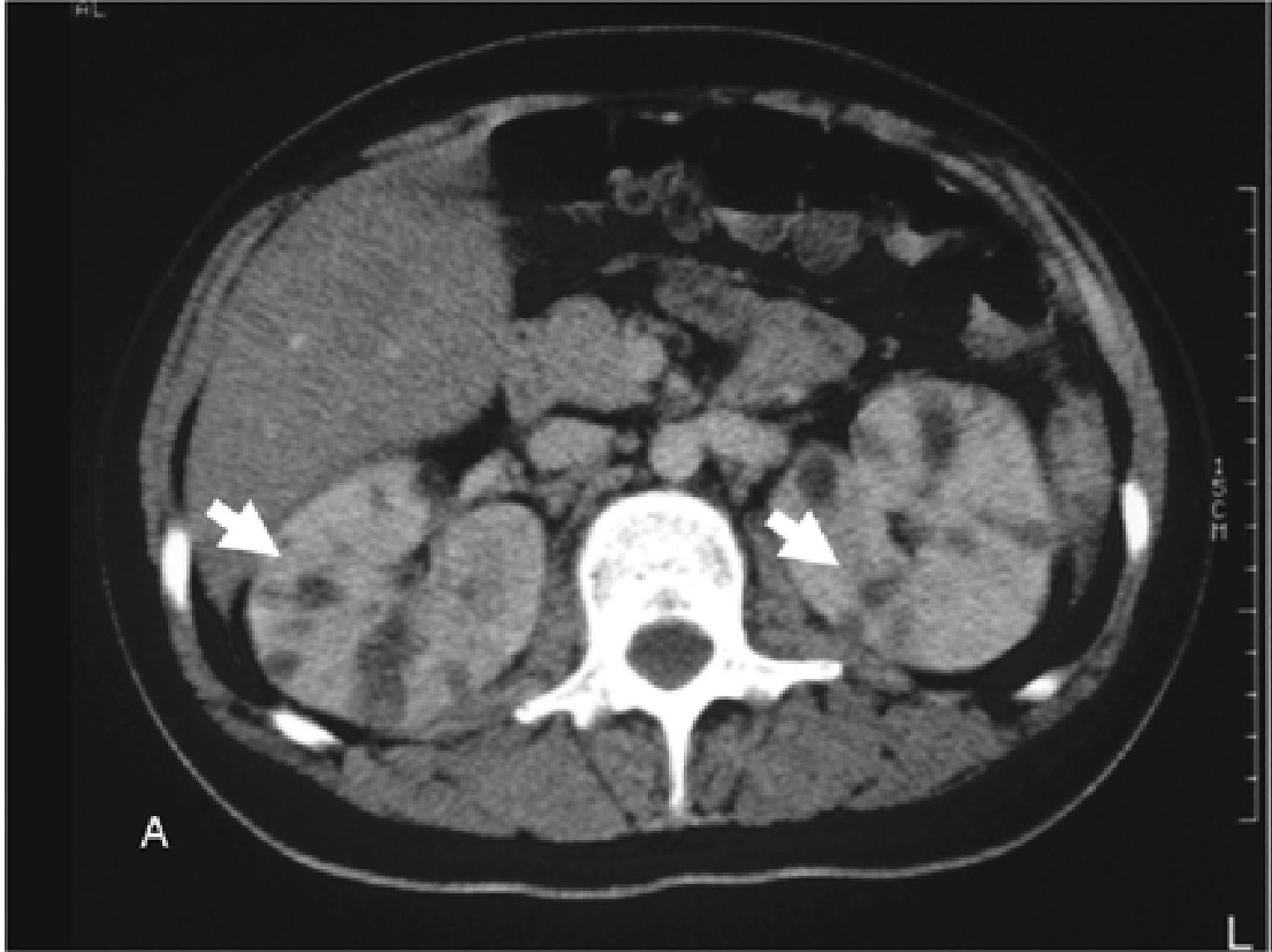
- **Incidence highest in smallest infants**
- **Diagnosed late**
- **High mortality**
- **Rising incidence**

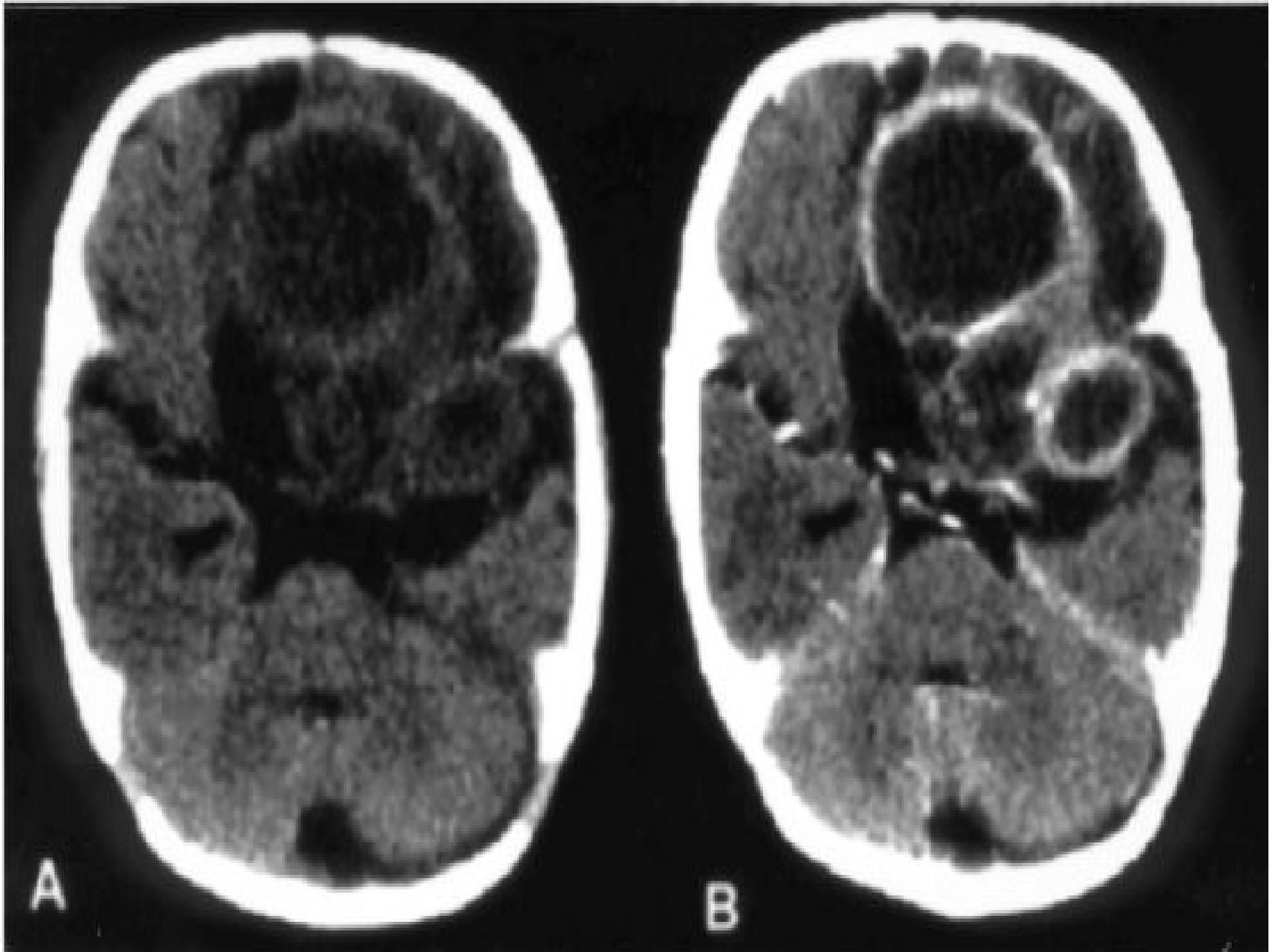
Invasive fungal infection in neonates

CLINICAL FEATURES

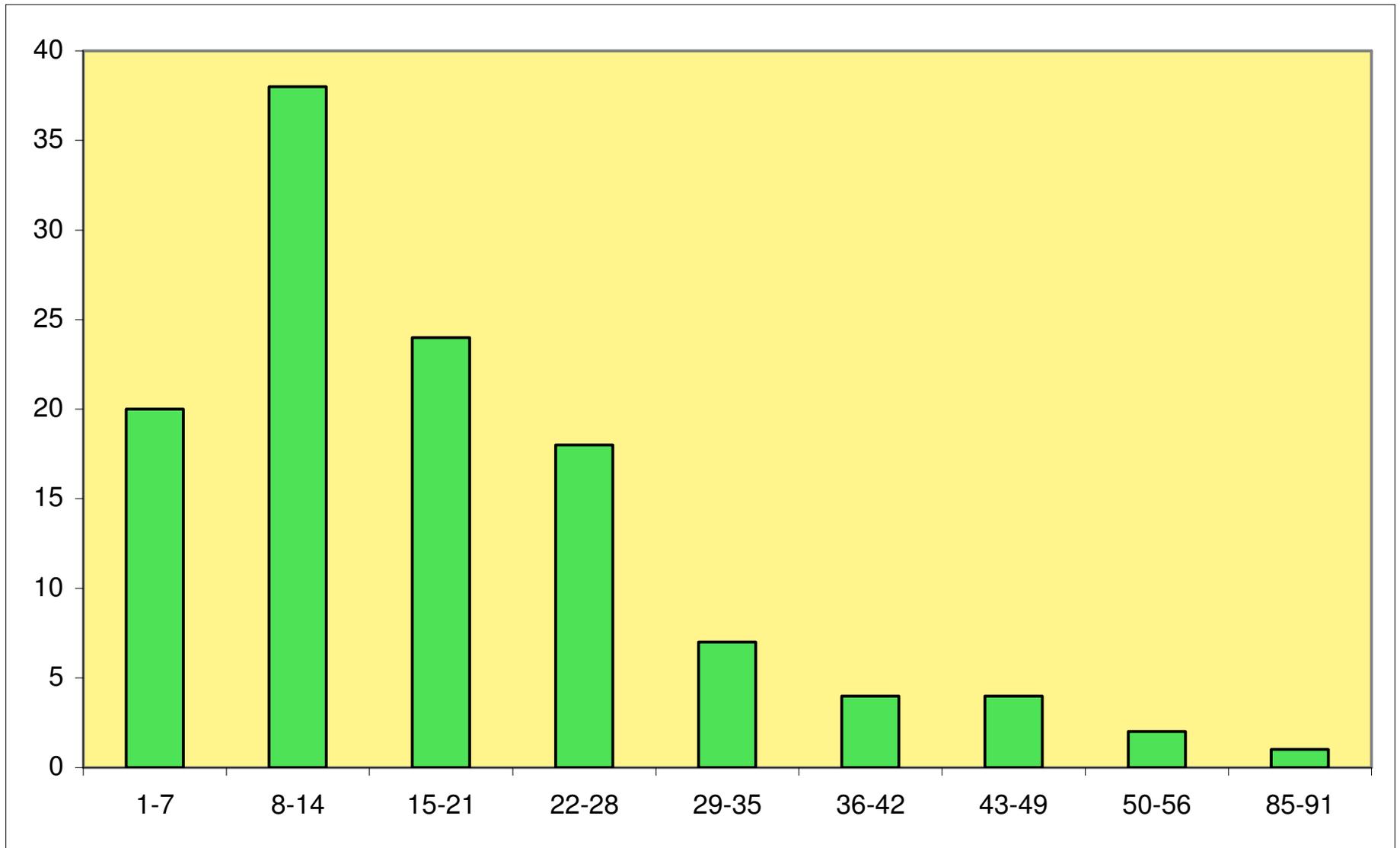








Age at culture diagnosis: median 15 days (range 1- 90)

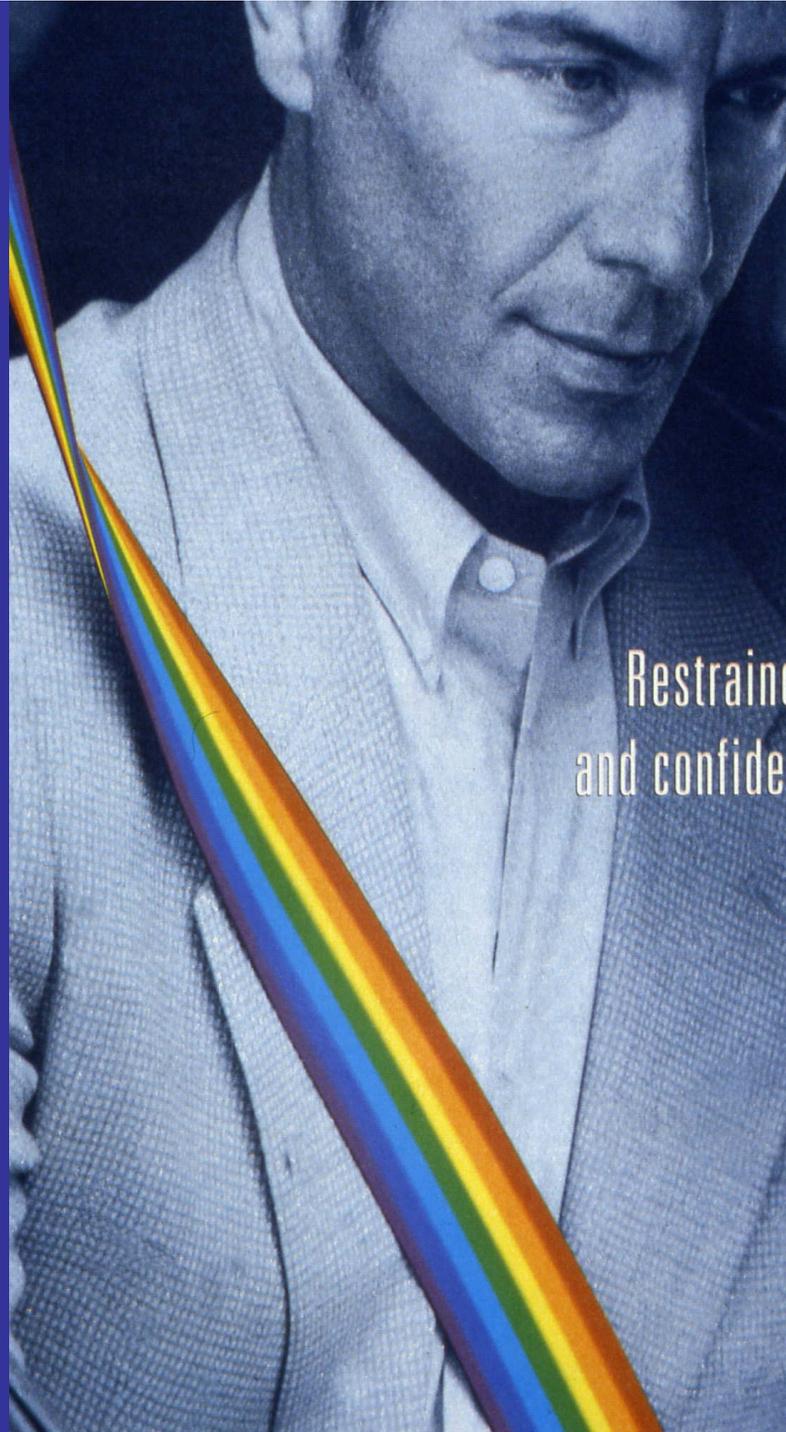


Haematological

- **Neutropenia common**
- **Commonest cause of neutropenia is IUGR**
- **For any septic neutropenic baby, bacterial sepsis more likely than fungal**

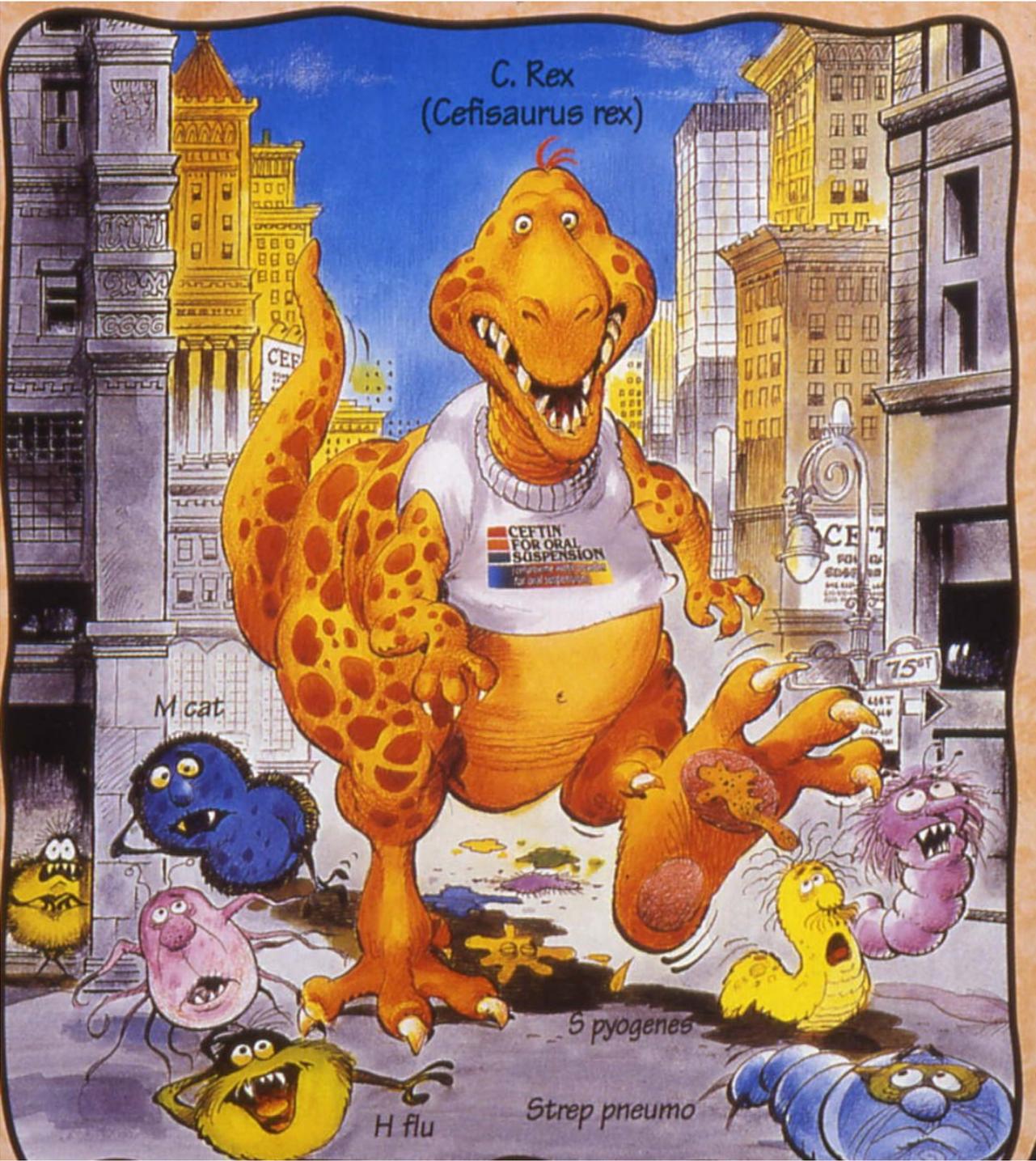
Risk factors

- **Broad spectrum antibiotics**
- **Prolonged parenteral nutrition**
- **Central venous catheters**
- **Prolonged endotracheal intubation**
- **H2 blockers**
- **Fungal colonisation (especially heavy)**



Restrained
and confident

C. Rex
(Cefisaurus rex)



M cat

H flu

S pyogenes

Strep pneumo

Broad spectrum antibiotics

- **Cotton CM et al, Pediatrics 2006; 118: 717-22**
- **NICHHD study**
- **284 babies with invasive candidiasis**
- **Third generation cephalosporin exposure:
RR 2.2 (95% CI 1.4-3.3)**

Early enteral feeding

- **Rapid enteral feeds (median <12.5 days) or
Slow enteral feeds (median >12.5 days)**

- **Reduced incidence of late-onset bacterial sepsis in babies fed earlier:**

14.0% vs 20.4%

P=0.002

- **No data on fungal infections**
- **Fewer central lines**

Invasive fungal infection in neonates

INCIDENCE

ASGNI

Prospective, multi-center study of systemic sepsis in Australasian neonates

23 hospitals contributed since 1992

Invasive fungal infection

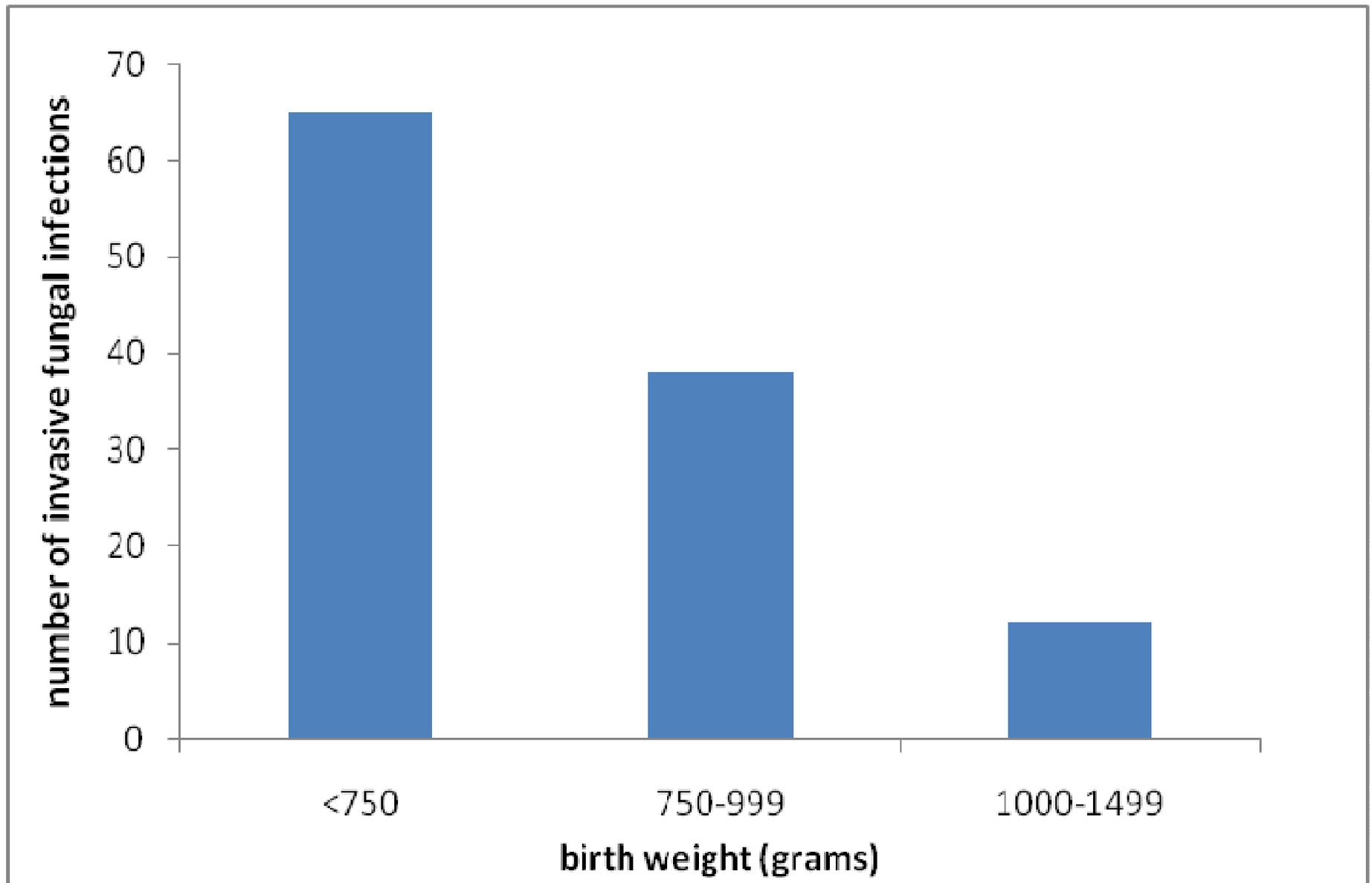
Positive blood +/- CSF culture (or raised CSF WBC)

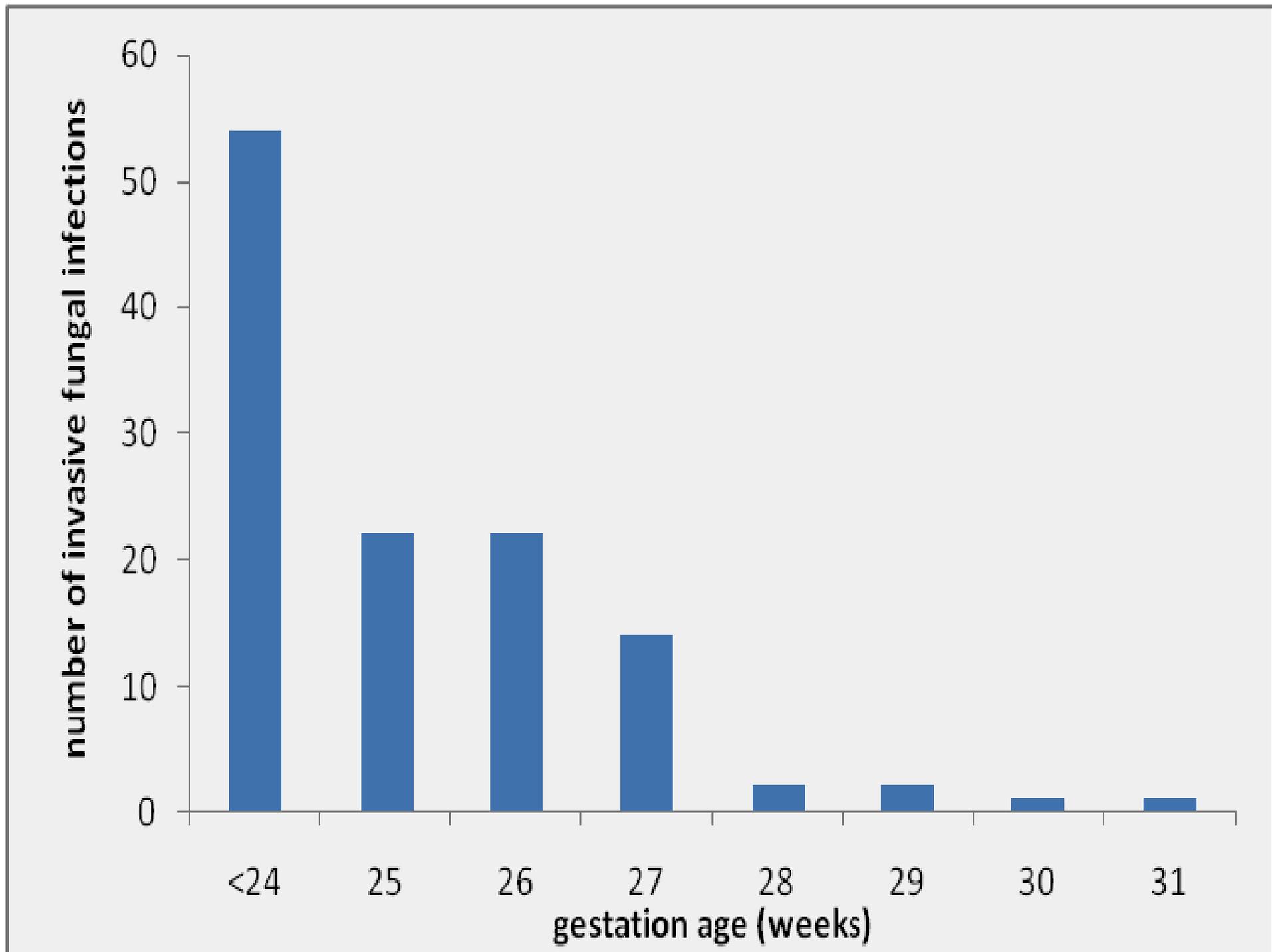
Babies <1500g

1993 - 2006

15 hospitals - median 7.5 per year (range 4 - 11)

Invasive fungal infection by birth weight: ASGNI, 1993-2006





Incidence of fungal infection

<1500g:

118 of 14,788 = 0.82% (95% CI 0.66-0.95%)

<1000g:

106 of 5,968 = 2.02% (95% CI 1.92-2.12%)

International studies

Country	Year	Definition	Birth weight	Incidence
USA¹	1998 - 2001	Blood & CSF	<1000g	7.7%
Italy²	2004 - 2005	Blood & CSF	<1500g	9.4%
UK³	2003	Blood, CSF, urine + others	<1500g <1000g	1.0% 2.1%
Australia + NZ⁴	1993 - 2006	Blood & CSF	<1500g <1000g	0.8% 2.0%

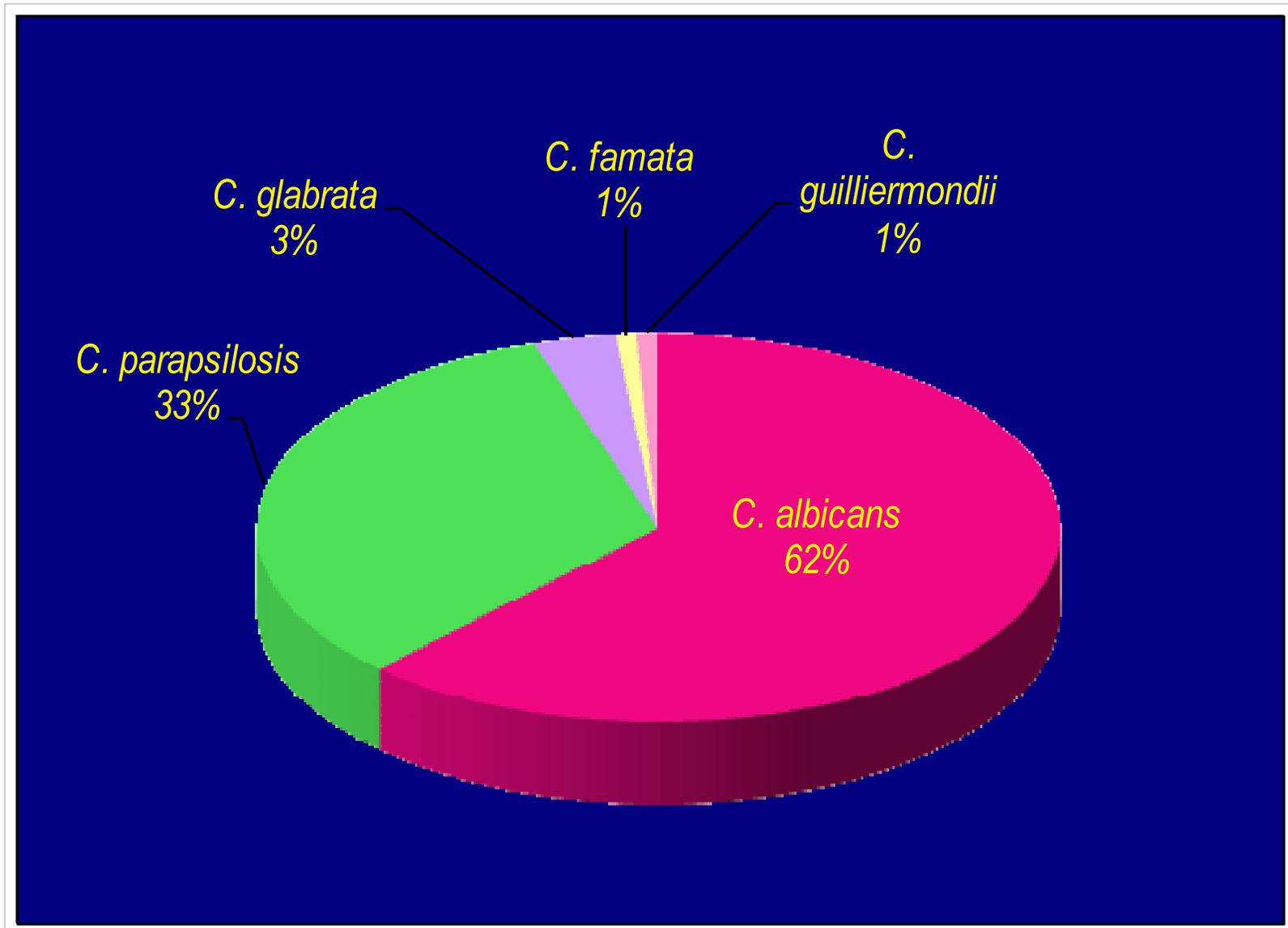
¹Benjamin, 2006

²Manzoni, 2007

³Clerihew, 2005

⁴ASGNI, 2008

Species variation



Invasive fungal infection in neonates

ANTIFUNGAL PROPHYLAXIS

Which prophylaxis?

- **Fluconazole**
- **Amphotericin**
- **Oral nystatin**

Fluconazole prophylaxis

- **Azole antifungal: well absorbed**
- **Given (oral or IV) for**
 - 30 days to babies <1500g
 - 45 days to babies <1000g
- **Selective chemoprophylaxis:**
 - <1500g if on broad spectrum antibiotics >3days
 - third generation cephalosporin
 - Colonised with Candida

Randomised placebo controlled trials of fluconazole: invasive fungal infection

	Fluconazole	Placebo	TOTAL
Infected	10 (3.1%)	30 (14.2%)	40
Not infected	315	181	496
TOTAL	325	211	536

Relative risk 0.23 (95% CI 0.11, 0.46)

Randomised placebo controlled trials of fluconazole: death from all causes

	Fluconazole	Placebo	TOTAL
Died	27 (8.5%)	30 (14.6%)	57
Survived	292	176	468
TOTAL	319	206	525

Relative risk 0.61 (95% CI: 0.37, 1.03)

Evidence regarding fluconazole

- **Fluconazole prevents fungal infections**
- **Trend to saving lives**
- **High incidence: NNT <1500g = 8 (5-20)**
- **Low incidence: NNT = 125 (or 45 <1000g)**

Fluconazole: safety concerns

Hepatotoxic

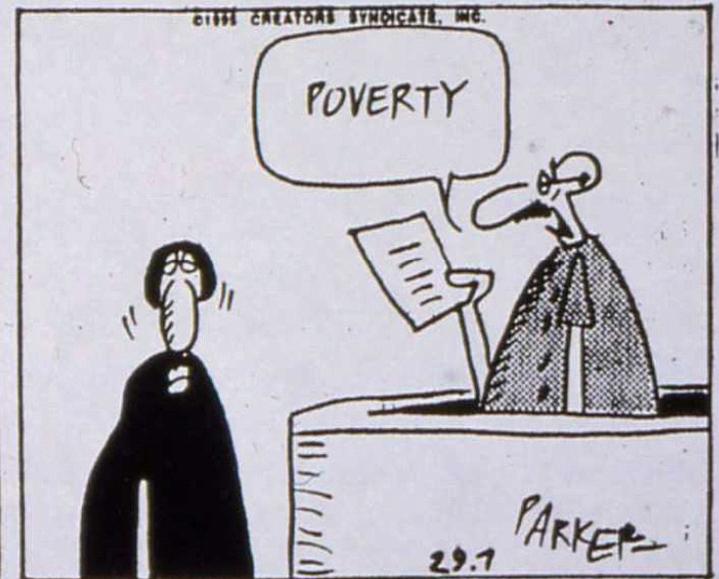
May induce resistance

Selection of non-albicans Candida

Amphotericin B

- **Much more toxic**
- **Much more expensive**

WIZARD OF ID BY PARKER AND HART



Oral nystatin

- **Polyene antifungal**
- **Not absorbed from GI tract**
- **Reduces colonisation**
- **Given orally 1mL 8-hourly until well**

Nystatin prophylaxis

[Sims ME et al, Am J Perinatol 1988; 5: 33-36]

- **Babies <1250g**
- **Oral nystatin 100,000U in 1 mL, 8-hourly**

33 treated: 4 colonised (12%); 2 sepsis (6%)

34 control:15 colonised (44%);11 sepsis (32%)

ASGNI, 1993-2006

Oral nystatin prophylaxis

[Howell A et al. ADC(F&N) 2009; 94: F429-33.]

Incidence <1500g

Yes 0.54%

No 1.23%

P<0.0001

Incidence <1000g

Yes 1.23%

No 2.67%

P<0.0001

Three hospitals changed policy

Incidence <1500g

Yes 0.69%

No 1.13%

$P > 0.05$

Incidence <1000g

Yes 1.23%

No 3.25%

$P < 0.005$

Meta-analysis

Invasive fungal infections <1500g

- **Fluconazole (6.6%) vs. placebo (16.6%)**
RR = 0.37 (95% CI 0.24-0.56)
- **Oral nystatin (5.3%) vs. placebo (32.9%)**
RR = 0.16 (0.11-0.23)
- **Fluconazole (4.1%) vs. oral nystatin (7.3%)**
RR = 0.56 (95% CI 0.20-1.60)

Conclusions

- **Reduce broad spectrum antibiotic use**
- **Reduce third generation cephalosporin use**
- **Early enteral feeds, catheters out, less TPN**
- **Antifungal prophylaxis is effective: use it**
- **Nystatin may be as good as fluconazole**
- **Use nystatin when incidence low or cost an issue**

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