ISSUES IN CRITICAL CARE AND HIV

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Overview

- Epidemiology of HIV-infected patients in ICU
- Case presentation
- HIV-related lung disease and ARF
- Management of ARF in HIV – what's new?
- Outcome of HIV-related ARF

Epidemiology of HIV-infected patients in ICU

- Era 1: 1981-1985 PCP, high mortality, poor post hospital survival
  - Decreased ICU admissions for AIDS - futility
- Era 2: 1986-1988 Adjunctive cortico-steroids, lower mortality rates
- Era 3: 1989-1991 Increased ICU mortality
  - Renewed optimism and ↑ ICU admissions

Morris Crit Care Med 2006;34:42-49

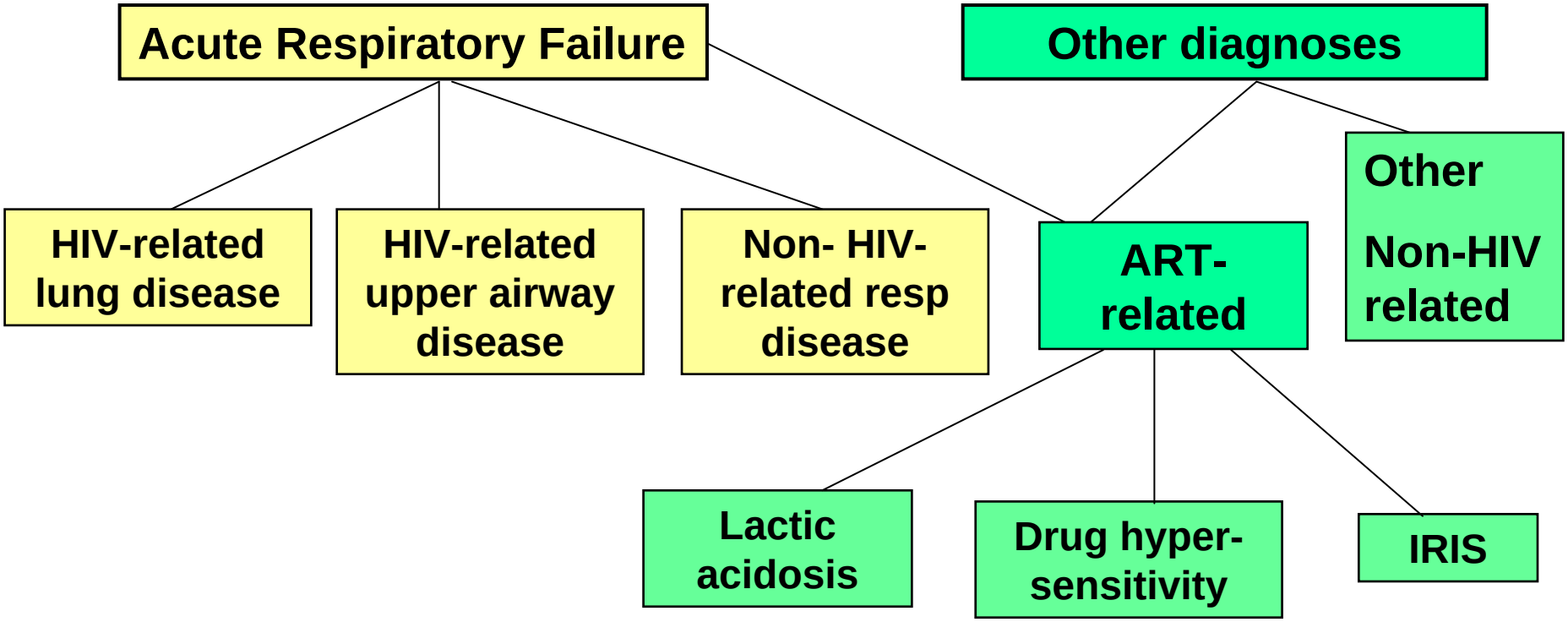
Epidemiology of HIV-infected patients in ICU 2

- Era 4: 1992-1995 stable admission rates, improved mortality (37%)

- Era 5: 1996 to present ART era
  - Decreased mortality – non-AIDS-associated Dx
  - Decreased ICU admissions

Morris Crit Care Med 2006;34:42-49

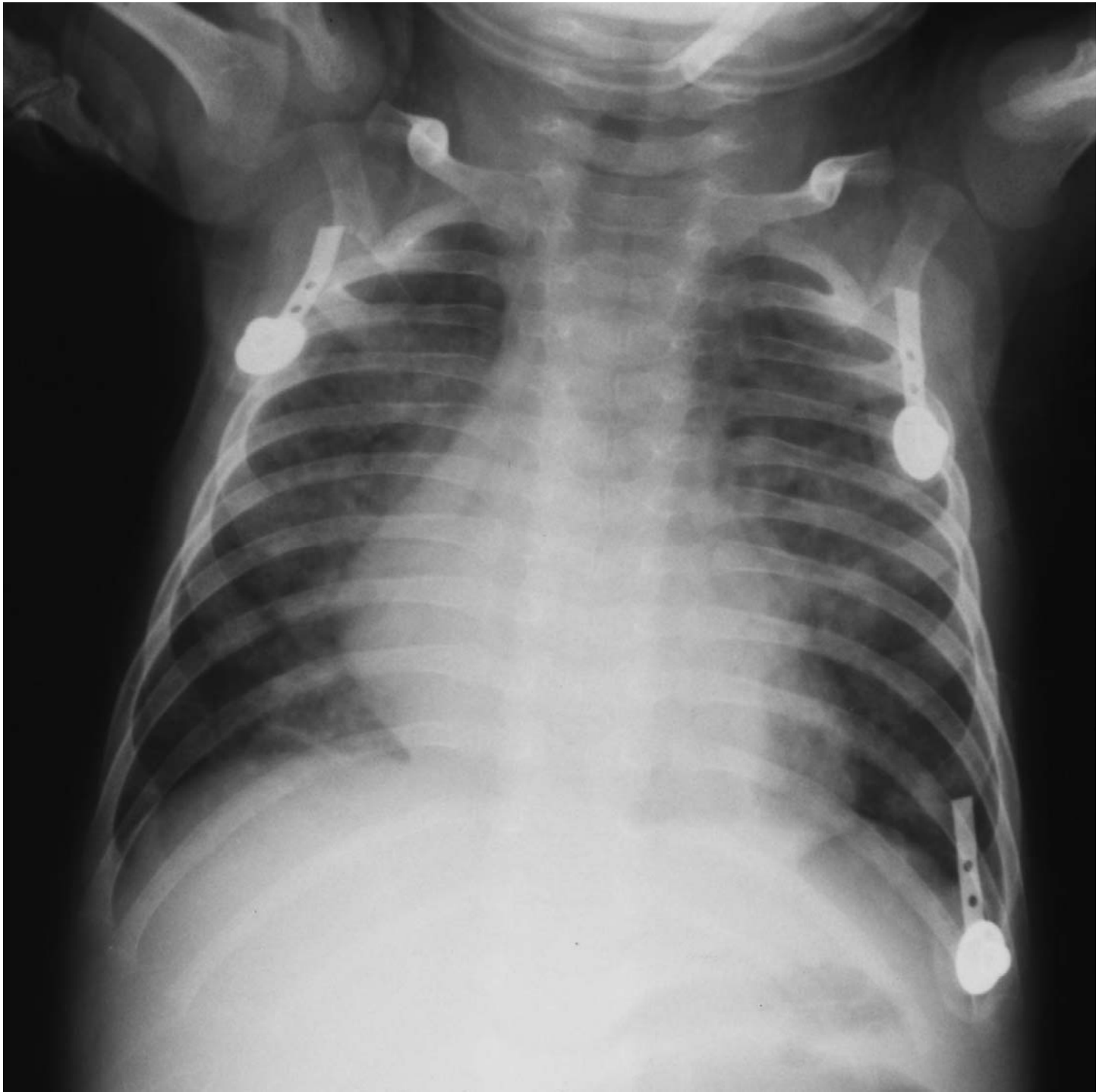
ICU admissions and HIV



Morris Crit Care Med 2006;34:42-49

Case presentation: Bongi

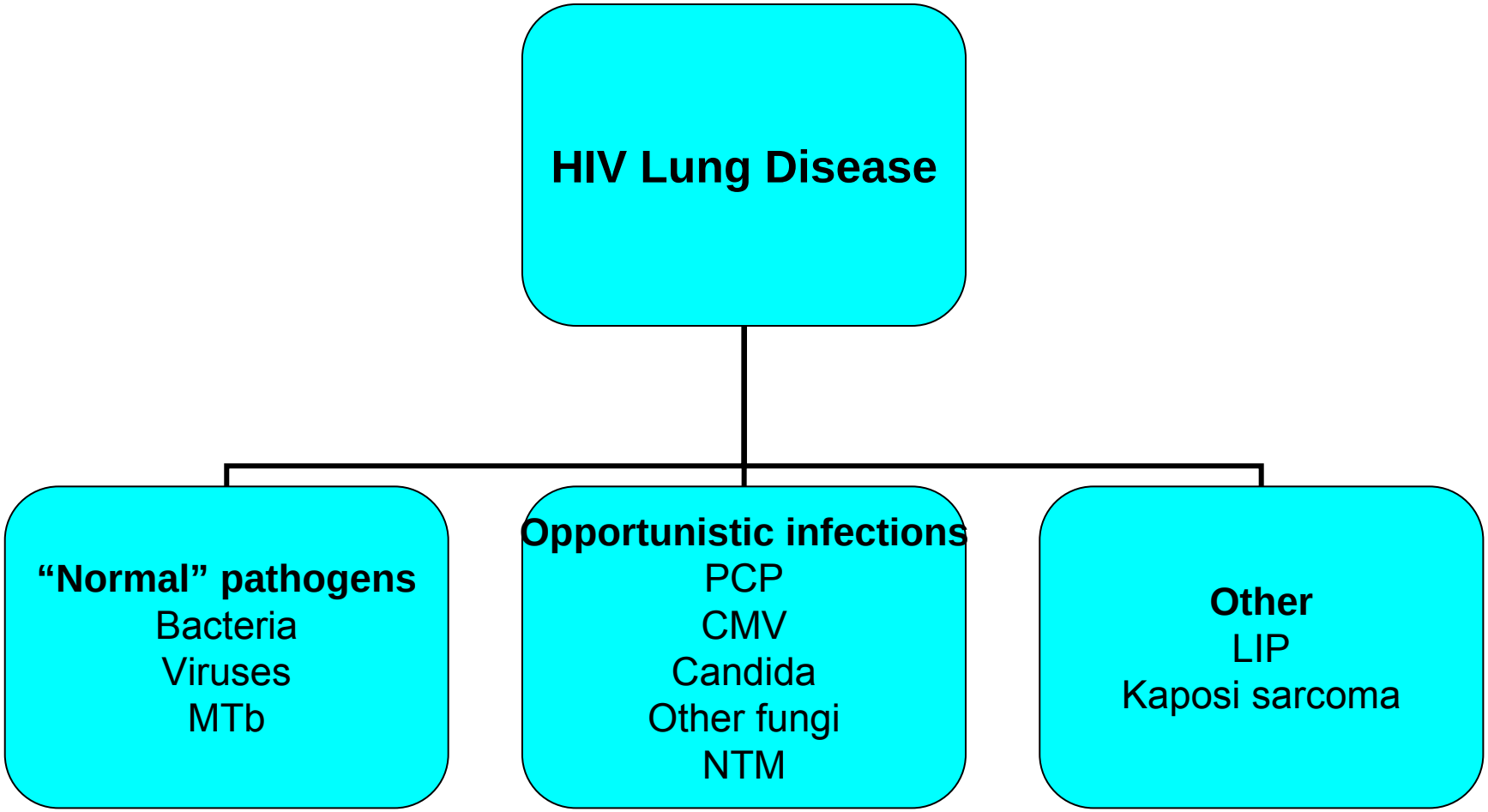
- 3-month-old baby girl
- Mother not tested antenatally
- Admitted to private hospital with pneumonia, oral thrush and anaemia
- HIV Elisa positive; CD4 150; viral load > 500 000 RNA copies/ml
- CXR: bilateral pneumonia, presumed *Pneumocystis jiroveci*



Bongi 2

- Rx: IV cefuroxime; IV cotrimoxazole; oral steroids; NPO_2
- Course: pyrexia: antibiotics changed
- Rx for PTB commenced 10 days after admission
- HAART: AZT, 3TC, Nelfinavir

HIV-related lung disease and ARF



Common causes of respiratory infection in HIV-infected African children

Bacterial pneumonia Strep pneumoniae H Influenzae Staph aureus Klebsiella spp Salmonella spp E coli	All ages	Increased incidence Increased antibiotic resistance
PCP P jiroveci	2-6 months	Poor outcome, esp with CMV
Viral pneumonia RSV CMV	 Infants Infants	 2^0 bacterial pneumonia; high mortality May co-exist with PCP
LIP	> 1 year	Confused w Tb; ?EBV
PTB (MTb)	All ages	Dx difficult

Graham SM Br Med Bull 2002;61:133-150; Int J TLD 2005;9:592-602

TABLE 1— Impact of Highly Active Antiretroviral Therapy (HAART) on Opportunistic Respiratory Infections

Infection	Pre-HAART rate[9]		Post-HAART rate[6]	
	Incidence rate per 100 child years	95% confidence interval	Incidence rate per 100 child years	95% confidence interval
Pneumocystis pneumonia	1.3	1.1–1.6	0.1	0.04–0.2
Bacterial pneumonia	11.1	10.3–12.0	2.2	1.8–2.6
Bacteremia	3.3	2.9–3.8	0.4	0.2–0.5
Disseminated *M. avium intracellulare complex*	1.8	1.5–2.1	0.1	0.1–0.3
Tracheobronchial or esophageal candidiasis	1.2	1.0–1.5	0.1	0.03–0.2

Zar Ped Pulm 2008;43:1-10

Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study

Lisa M McNally, Prakash M Jeena, Kavitha Gajee, Stanley A Thula, A Willem Sturm, Sharon Cassol, Andrew M Tomkins, Hoosen M Coovadia, David Goldblatt

358 children, 1-59 months

WHO-defined severe or very severe pneumonia

Rx Benzylpenicillin + gentamicin + high dose TMP-SMX

Primary outcome: treatment failure at 48 h

McNally Lancet 2007;369:1440-51

	Younger than 1 year				1 year and older			All children (n=358)
	HIV+ (n=170)	HIV-EU (n=41)	HIV- (n=49)	All under 1 year (n=260)	HIV+ (n=72)	HIV- (n=26)	All over 1 year (n=98)	
Streptococcus pneumoniae	12 (7%)	0	1 (2%)	13 (5%)	12 (17%)	1 (4%)	13 (13%)	26 (7%)
Staphylococcus aureus	7 (4%)	2 (5%)	2 (4%)	11 (4%)	4 (6%)	1 (4%)	5 (5%)	16 (5%)
Viridans group streptococci	6 (4%)	3 (7%)	2 (4%)	11 (4%)	2 (3%)	2 (8%)	4 (4%)	15 (4%)
Streptococcus milleri	2 (1%)	0	0	2 (1%)	1 (1%)	0	1 (1%)	3 (1%)
Enterococcus faecalis	0	0	1 (2%)	1 (<1%)	1 (1%)	0	1 (1%)	2 (1%)
Other streptococci	5 (3%)	2 (5%)	4 (8%)	11 (4%)	1 (1%)	0	1 (1%)	12 (3%)
Escherichia coli	2 (1%)	1 (2%)	0	3 (1%)	0	0	0	3 (1%)
Haemophilus influenzae	1 (<1%)	1 (2%)	0	2 (1%)	0	0	0	2 (1%)
Klebsiella pneumoniae	1 (<1%)	1 (2%)	0	2 (1%)	0	0	0	2 (1%)
Serratia marcescens	1 (<1%)	0	0	1 (<1%)	0	0	0	1 (<1%)
Pseudomonas aeruginosa	0	1 (2%)	0	1 (<1%)	0	0	0	1 (<1%)
Acinetobacter baumii	1 (<1%)	0 (0)	0	1 (<1%)	0	0	0	1 (<1%)
Campylobacter coli	1 (<1%)	0	0	1 (<1%)	0	0	0	1 (<1%)
Salmonella spp	1 (<1%)	0	0	1 (<1%)	0	0	0	1 (<1%)
Candida albicans	0	0	1 (2%)	1 (<1%)	0	0	0	1 (<1%)
No significant organism	133 (78%)	32 (78%)	39 (80%)	204 (79%)	52 (72%)	23 (89%)	75 (76%)	278 (78%)

All data are number (%). HIV-1⁻=HIV uninfected. HIV-1^{EU}=HIV exposed, uninfected. HIV-1⁺=HIV infected. *Eight children had two organisms isolated from their admission blood culture. Therefore numbers do not add up to 358.

Table 3: **Admission blood culture results by HIV status and age***

McNally Lancet 2007;369:1440-51

	Younger than 1 year				1 year or older		
	Total (n=90)	Infected (n=74)	Exposed uninfected (n=9)	Uninfected (n=7)	Total (n=20)	Infected (n=13)	Uninfected (n=7)
Pneumocystis jirovecii	29 (32%)	26 (35%)	3 (33%)	0	0	0	0
Mycobacterium tuberculosis	15 (17%)	13 (18%)	0	2 (29%)	9 (45%)	5 (39%)	4 (57%)
Cytomegalovirus	40 (45%)	37 (51%)	2 (22%)	1 (14%)	4 (20%)	3 (23%)	1 (14%)
Streptococcus pneumoniae	9 (10%)	7 (9%)	0	2 (29%)	3 (15%)	3 (23%)	0
Staphylococcus aureus	13 (14%)	11 (15%)	2 (22%)	1 (14%)	6 (30%)	4 (31%)	2 (29%)
Other gram positive	6 (7%)	5 (7%)	0	1 (14%)	3 (15%)	3 (23%)	0
Haemophilus influenzae	5 (6%)	3 (4%)	1 (11%)	1 (14%)	4 (20%)	2 (15%)	2 (29%)
Klebsiella pneumoniae	9 (10%)	8 (11%)	1 (11%)	0	0	0	0
Escherichia coli	8 (9%)	7 (9%)	1 (11%)	0	0	0	0
Salmonella spp	1 (1%)	1 (1%)	0	0	0	1 (8%)	0
Legionella spp	1 (1%)	1 (1%)	0	0	0	0	0
Other gram negative	10 (11%)	8 (11%)	1 (11%)	1 (14%)	3 (15%)	2 (15%)	1 (15%)
Adenovirus	6 (7%)	4 (5%)	0	2 (28%)	3 (15%)	2 (15%)	1 (14%)
Respiratory syncytial virus	11 (12%)	8 (11%)	3 (33%)	0	2 (10%)	0	2 (29%)
Other virus	8 (9%)	6 (8%)	1 (11%)	1 (14%)	3 (15%)	3 (23%)	0
Aspergillus spp	0	0	0	0	1 (5%)	1 (8%)	0
Streptomyces spp	1 (<1%)*	1 (<1%)	0	0	0	0	0
Sacchromyces spp	0	0	0	0	1 (5%)	1 (8%)	0

All data are number (%). *Only children who had all study investigations and failed therapy are included (admission and non-responder blood culture; admission nasopharyngeal aspirate and NB-BAL or lung aspirate for viral immunofluorescence; and culture, induced sputum, and NB-BAL or lung aspirate for *P jirovecii* pneumonia and tuberculosis; gastric washings for tuberculosis; NB-BAL, lung aspirate, or pleural aspirate for bacteria). Bacteria isolated from nasopharyngeal swabs or induced sputa are not regarded as significant and therefore not included.

Table 5: **Organisms isolated from children who were investigated for failing to respond by HIV status and age**

McNally Lancet 2007;369:1440-51

Management of ARF in HIV

Standard Management

Antibiotics – Penicillin or Ampicillin + Gentamicin
(or other as appropriate)

+

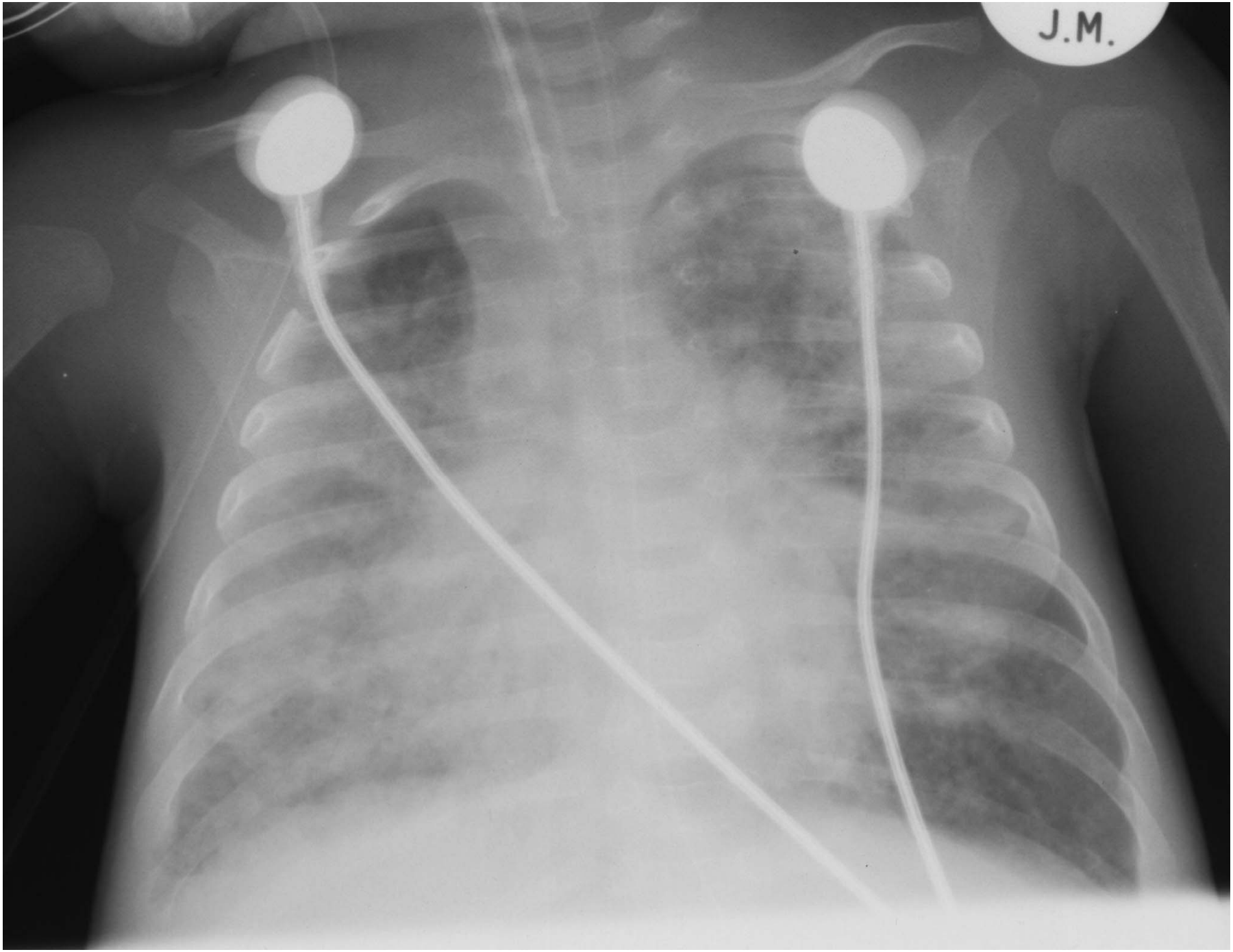
Trimethoprim-sulphamethoxazole

+

Steroids

Bongi 3

- Remained stable on NPO_2
- 14 days after admission: deterioration, failed nasal CPAP
- Intubated and commenced on conventional ventilation
- T/A: RSV, PCP, CMV all negative
- TB cultures outstanding
- Cause of lung disease?

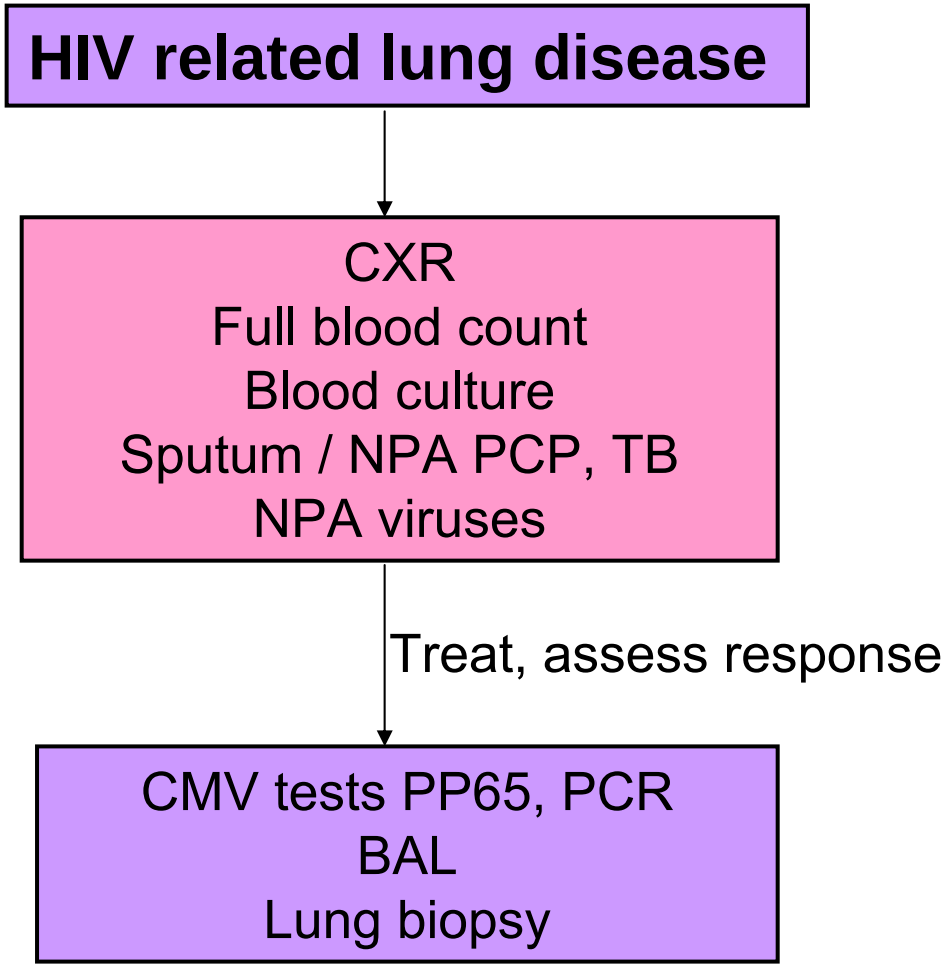

J.M.

Treatment failure (103/110 pts)

- No organism 7 (6%)
- 1 organism 24 (24%)
- 2 organisms 41 (40%)
- 3 organisms 22 (21%)
- 4 organisms 9 (9%)
- i.e. > 1 organism in 72 (70%) children
- 66/97 no bacteria on NB-BAL
- 59/66 virus, M Tb or P jiroveci

McNally Lancet 2007;369:1440-51

Approach to investigation



Bongi 4

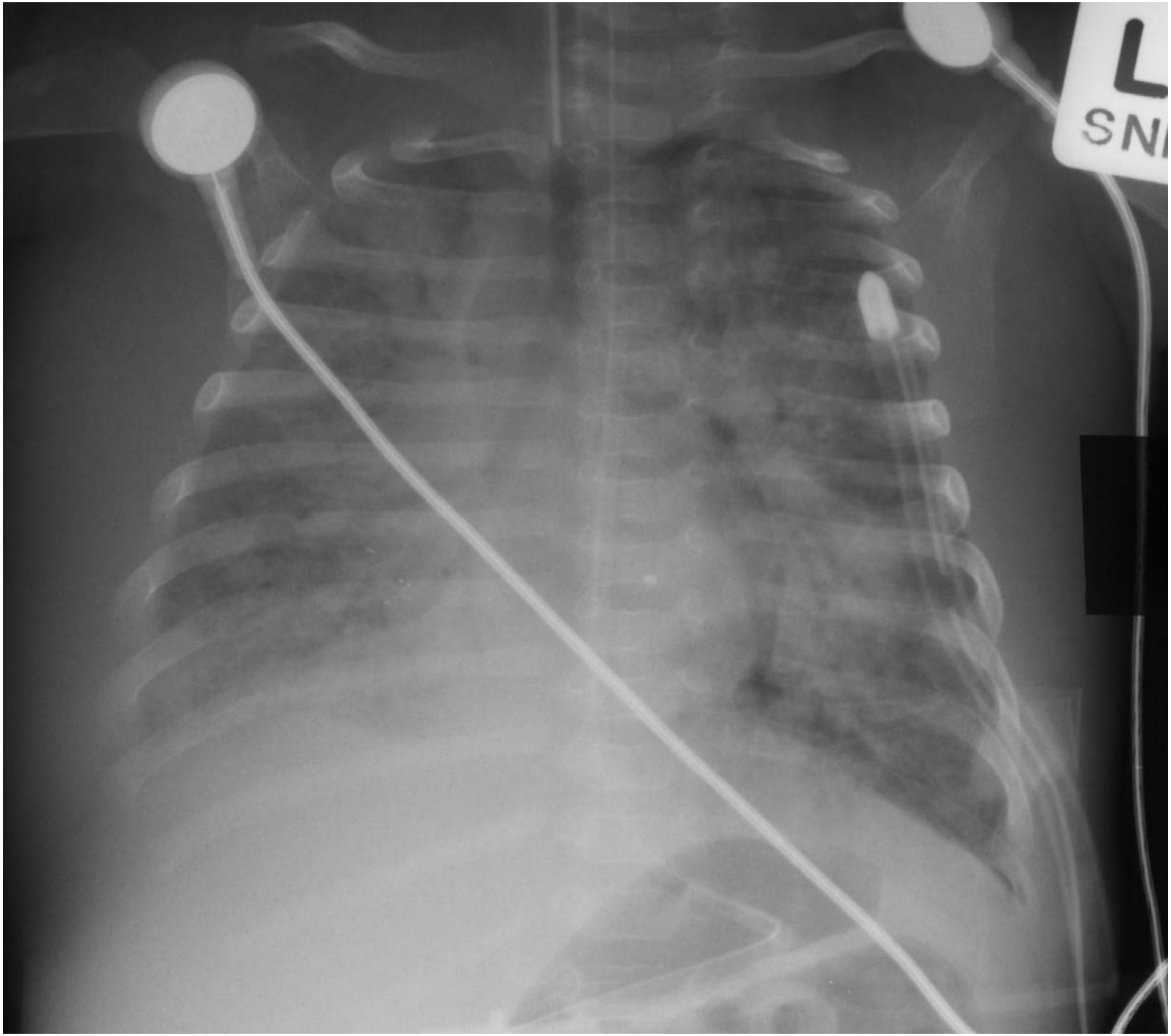
- Transferred to A9 PICU, Tygerberg Children's Hospital
- For lung biopsy

Bongi 5

- On admission findings consistent with severe immunosuppression and severe pneumonia
- HFOV instituted
- Lung biopsy 2 days later: most likely CMV
- Rx ganciclovir
- Histology: necrotising pneumonia; inclusions suggest CMV

Bongi 6

- HFOV continued; no real change
  - MAP 25; ΔP 50; Frequency 6.7 Hz; FiO_2 1.0
- Pneumothorax (L): ICD
- 7 days after lung biopsy immuno-histochemistry confirmed CMV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Bongi 7

- 3-month-old baby girl with AIDS and severe pneumonia, not responding to antibiotics, cotrimoxazole, steroids, ganciclovir and HAART
- Prognosis poor
- Value of continued treatment questionable
- Ventilation withdrawn: RCPCH “no chance” situation
- Resource consumption also an issue

Factors associated with poor prognosis in PCP

- Bacterial and viral co-infections
- Pneumothorax (p=0.003)*
- Prolonged need for ventilation
- Delayed institution of treatment

Jeena Arch Dis Child 2008;93:545

What is new in management of ARF in HIV?

Ganciclovir

- High prevalence of CMV colonisation in infants with PCP
- Risk of CMV pneumonitis
- UK study: add ganciclovir if colonised with CMV to reduce risk of invasive CMV disease
- If CMV status unknown – empiric addition of ganciclovir, discontinue if negative

Cooper Int Care Med 2004;30:113-8

ART: Initiate in ICU?

Potential problems

- Limited availability of IV or liquid meds
- Erratic GIT absorption subtherapeutic drug levels
- HI virus resistance
- IRIS
- Drug interactions
- Noncompliance after discharge

Potential benefits

- Immune reconstitution may improve prognosis
- Viral suppression during acute illness
- Decreased risk for subsequent opportunistic infections

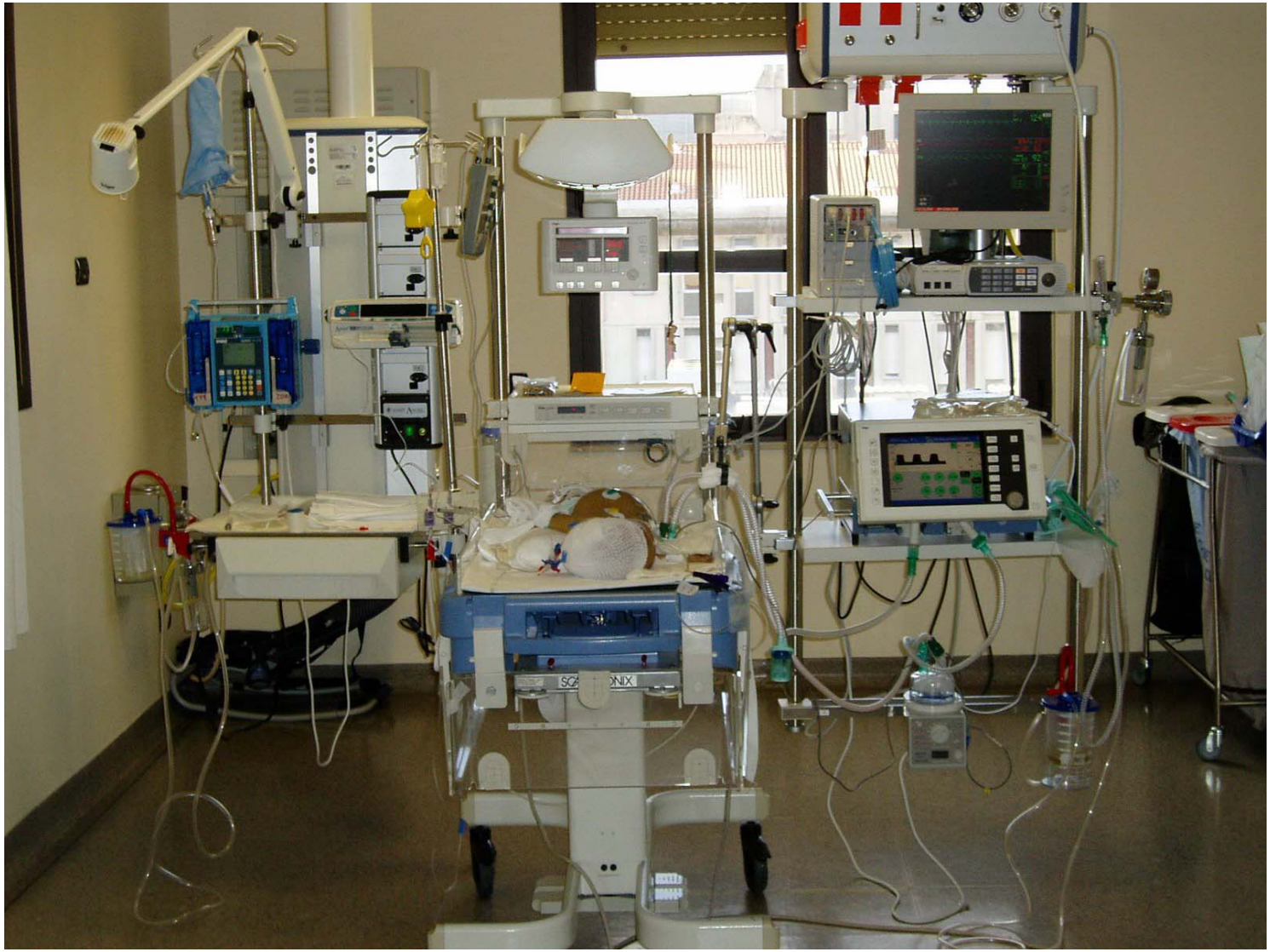
Morris Crit Care Med 2006;34:42-49

What's new in ventilation?

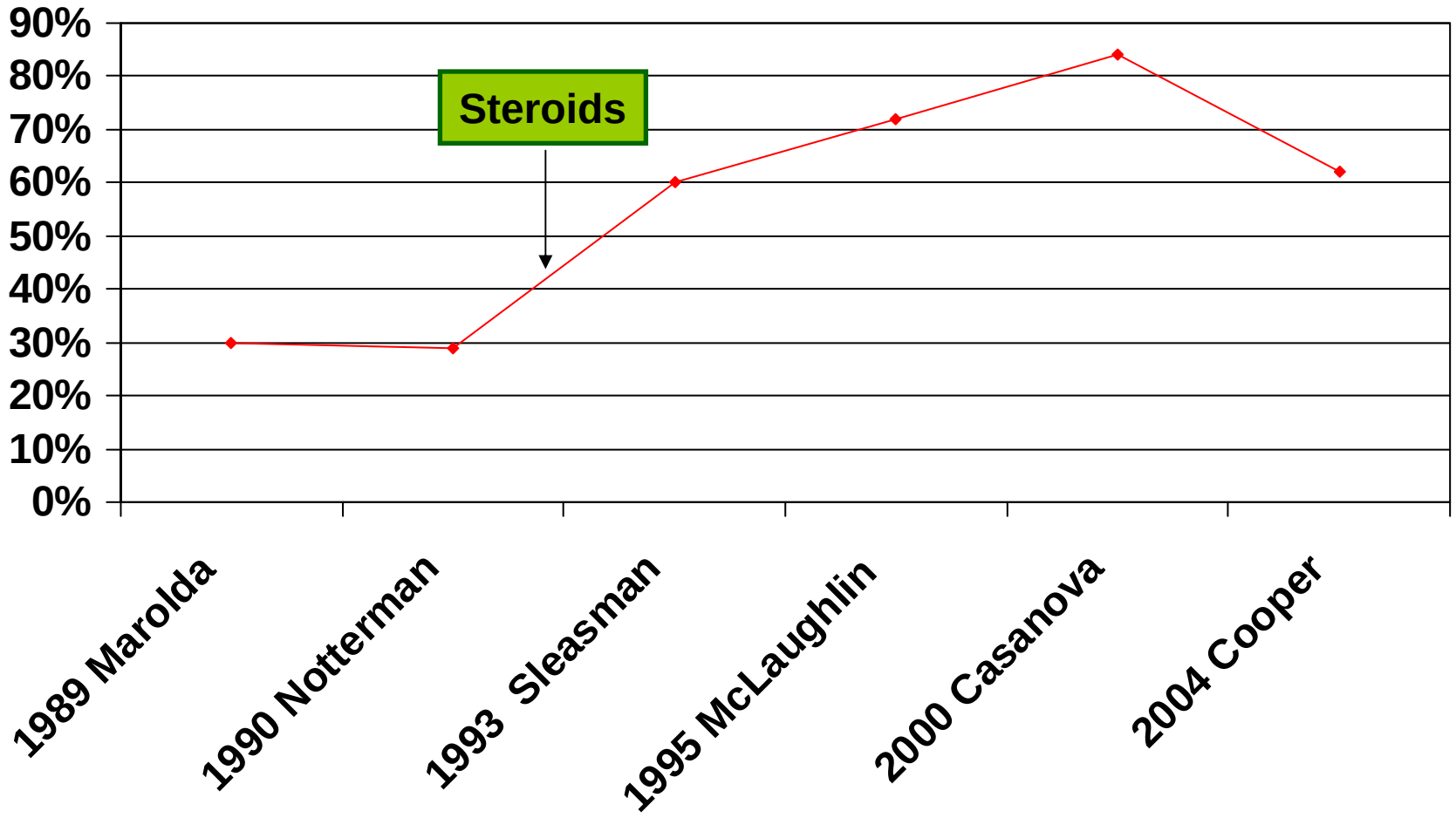
- Conventional ventilation
  - Low tidal volume ventilation associated with reduced mortality in adults infected with HIV

    – Davis Thorax Jun 2008
- HFOV

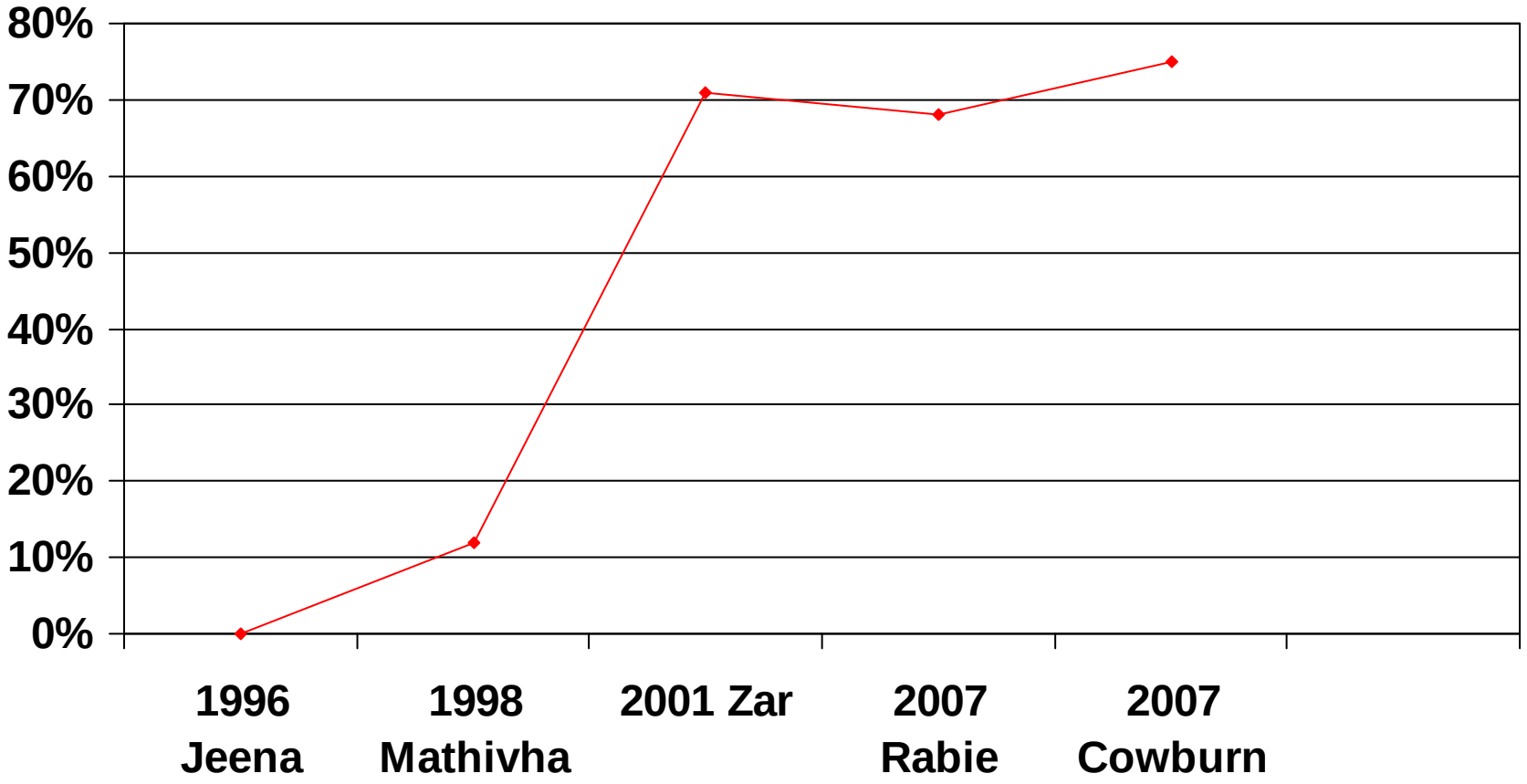
Outcome of ARF in HIV



ICU Survival of HIV-infected children with acute respiratory failure (ARF)



ICU Survival of HIV-infected children with ARF in SA



Long-term outcome

- 2002: 136 HIV-infected children RCCH
  - PICU survival 73%
  - Hospital discharge 46%
  - 1 year survival 14%

- 2004: 42 HIV-infected children St Mary's
  - PICU survival 62%
  - 1 year survival 50%

Cowburn Arch Dis Child 2007; Cooper 2004 Int Care Med

Long-term outcome 2

- 2003: 68 HIV-infected children RCCH
  - PICU survival 75%
    - PCP survival 75%
  - Hospital discharge 51%
  - HAART 31% (41% PICU survivors)
  - ±1 year survival 19% (25% PICU survivors)

Cowburn Arch Dis Child 2007

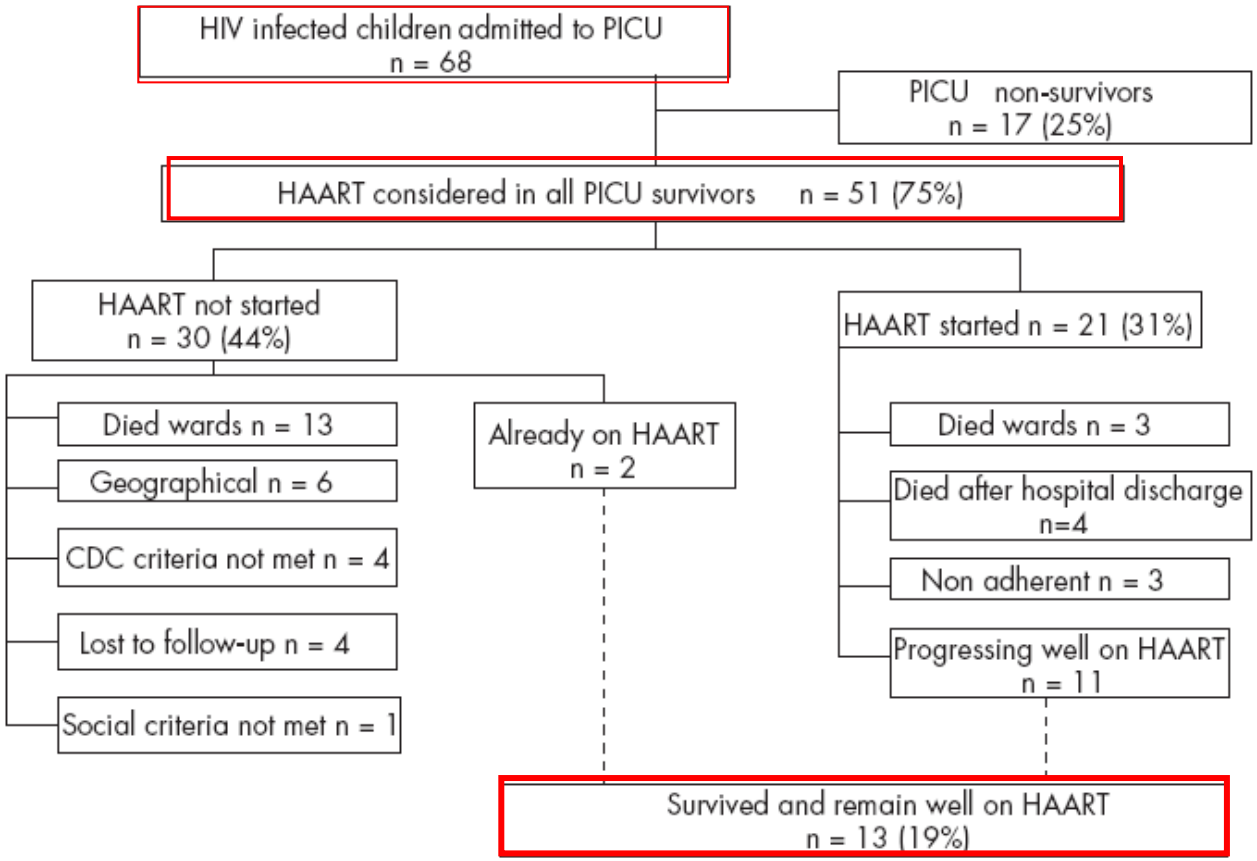
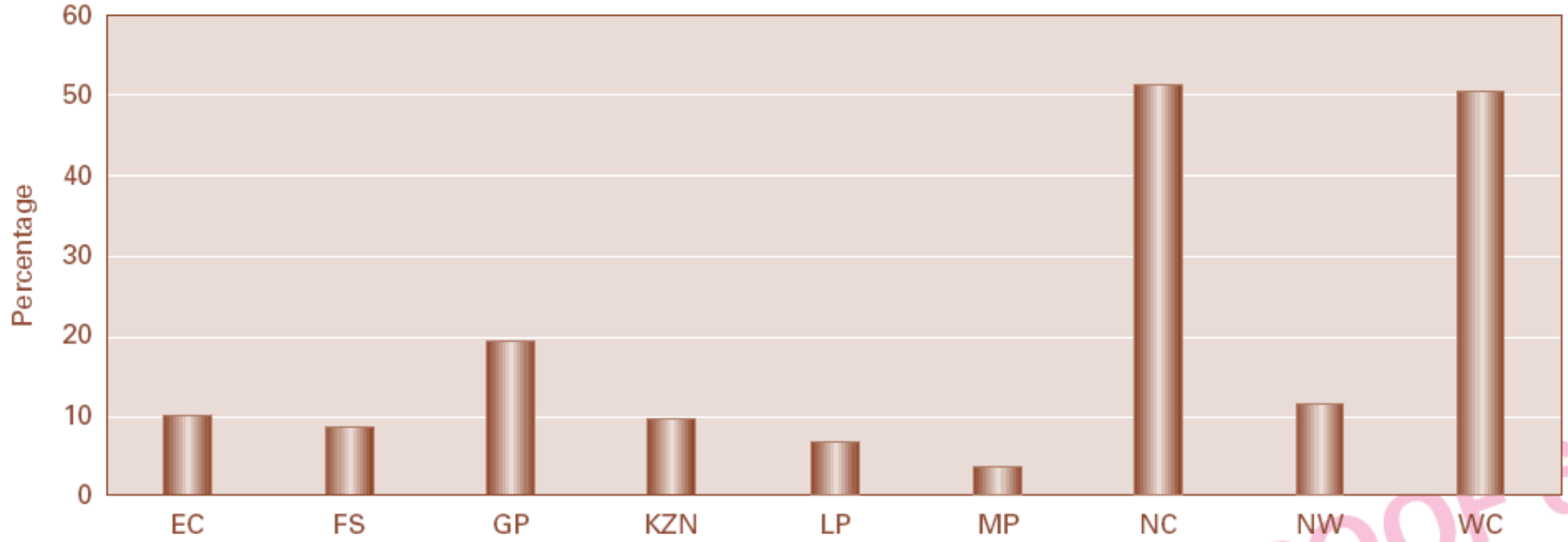


Figure 1 Critically ill HIV-infected children: survival and HAART.

Cowburn Arch Dis Child 2007

Estimated percentage of children with advanced HIV who are receiving ART[j]



Source: Data compiled from ASSA2003 (provincial output) mid-2005 estimates[11] and Table 3 above

Meyers Management of HIV-infected children 2007

Long-term outcome 3

- Microbiological records for PCP 2000 - 2002 at KE VIII
- 52 children, 38 HIV-infected, 5 HIV exposed uninfected, 9 excluded inadequate records
- At 2 years post PCP, 11/38 (28.9%) HIV-infected children not on HAART were alive

Jeena Arch Dis Child 2008;93:545

Summary

- Changing epidemiology of HIV in ICU
- Bacterial pneumonia commonest infectious cause of HIV-related lung disease
- In SA inadequate MTCT programme plus poor access to ART result in infants with PCP still being admitted for ventilation
- Apparent benefit from empiric early use of ganciclovir in very severe pneumonia

Summary 2

- Improved PICU survival suggests these children should not be denied ventilation
- Limited PICU beds and poor access to ART mitigate against admitting all HIV-infected children
- Policy should be developed that is reasonable and accountable