Neonatal Sepsis in India: Diagnosis and management guidelines

Delhi NeoCon Oct 2020

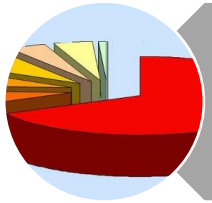
Outline

1. Diagnosis:
   - How to differentiate sepsis from common mimickers: role of clinical features, biomarkers (including sepsis screen)
   - Key step: must take blood culture before starting antibiotics
2. Prevention:
   - Remains the most critical step to reduce mortality: CFR remains higher even in those pathogens susceptible to antibiotics
   - Antibiotic stewardship: CDC guidelines
   - Creating unit specific antibiotic policy- to guide first line empiric therapy and beyond
   - Newer modalities: - probiotics, etc?

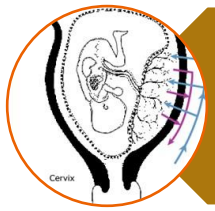
Outline

3. Treatment:
   - Empiric therapy→ definitive therapy
   - De-escalaltion; escalaltion: when and why
   - When to stop antibiotics: PCT vs expectant management
   - Choices in MDR empiric treatment
   - Duration of therapy
   - Status of adjunctive therapy- probiotics, etc?
   - Beyond antibiotics: key role of supportive therapy, barrier nursing, isolation
4. Key words and messages

Sepsis in India: Issues



High burden & case-fatality

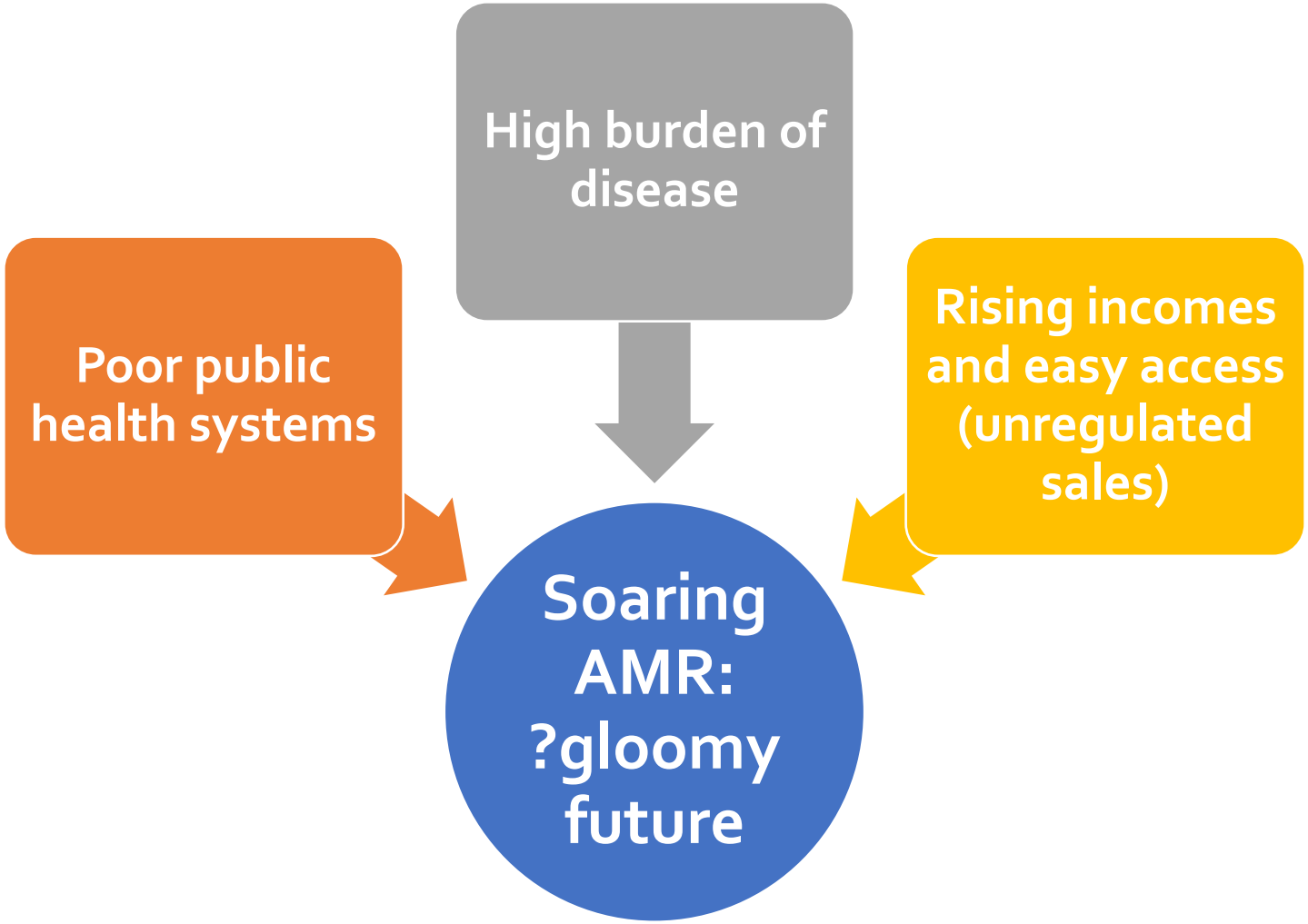


Early onset profile = late onset

Unreliable diagnosis

High antimicrobial resistance

Indian context- convergence of factors



How do we deal with this situation?

- **PREVENTION**, is naturally the key
- Therefore, today's time – *the time in hand*- is the best time to act

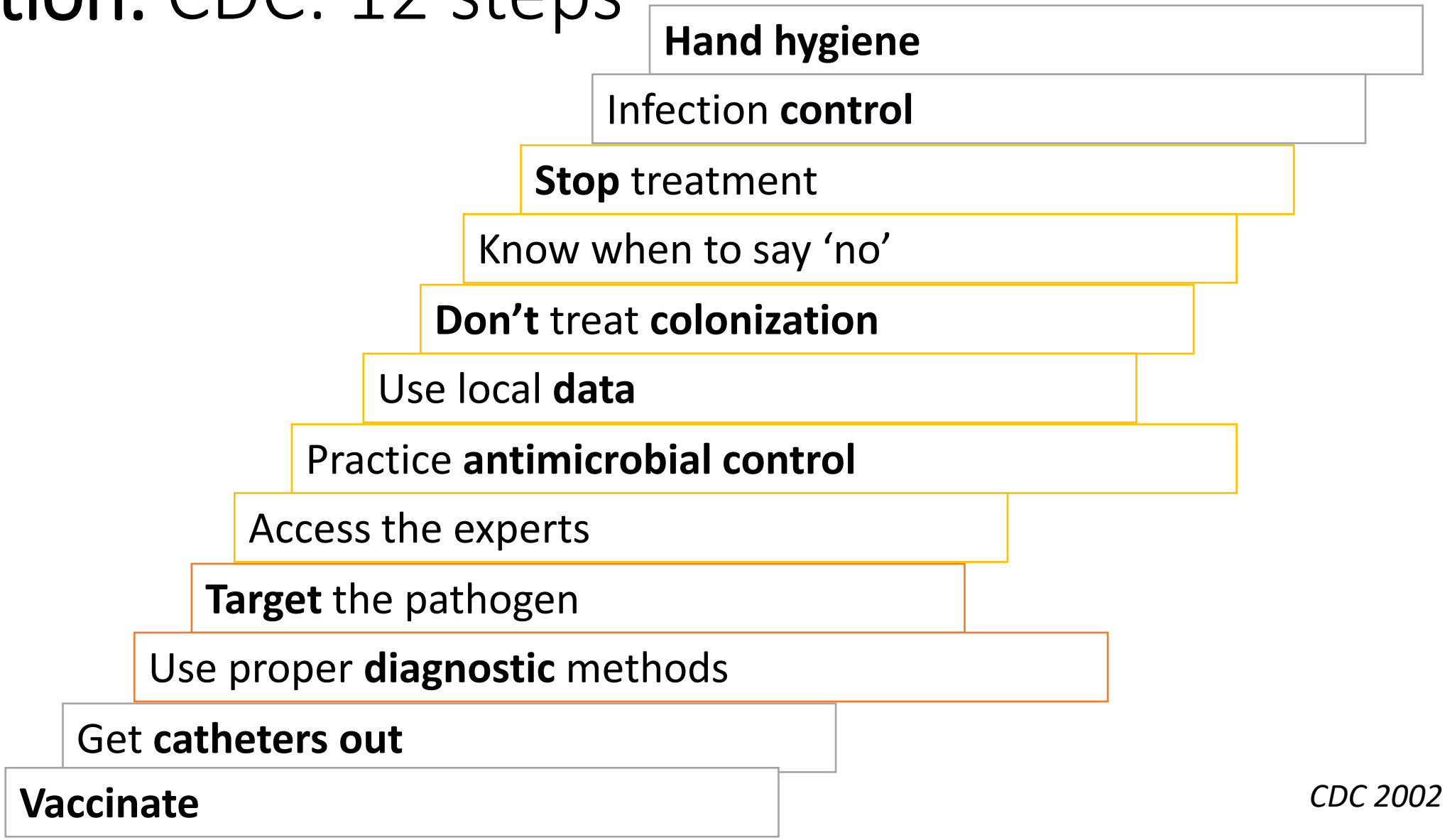
Prevention

Pathogens	Antimicrobial class	Resistance	CFR in culture positive sepsis due to	
			Resistant pathogens	Sensitive pathogens
Gram-negative				
Klebsiella spp. (n= 169)	ES cephalosporins	105/169 (62·1%)	57/104 (54·8%)	38/65 (58·4%)
	Carbapenems	59/169 (34·9%)	36/59 (61·0%)	59/110 (53·6%)
	MDR	91/169 (53·8%)	52/91 (57·1%)	43/78 (55·1%)
Acinetobacter spp. (n= 222)	ES cephalosporins	85/222 (38·3%)	59/85 (69·4%)	71/137 (51·8%)
	Carbapenems	174/222 (78·3%)	106 / 174 (60·9%)	24/48 (50·0%)
	MDR	181/222 (81·5%)	112/181 (61·8%)	18/41 (43·9%)
Escherichia coli (n= 137)	ES cephalosporins	65/137 (47·4%)	40/64 (62·5%)	43/73 (58·9%)
	Carbapenems	21/137 (15·3%)	12/21 (57·1%)	71/116 (61·2%)
	MDR	52/137 (37·9%)	30/52 (57·6%)	53/85 (62·3%)
Pseudomonas spp. (n= 68)	ES cephalosporins	32/68 (47·0%)	29/32 (90·6%)	24/36 (66·6%)
	Carbapenems	21/68 (30·8%)	19/21 (90·4%)	34/47 (72·3%)
	MDR	13/68 (19·1%)	11/13 (84·6%)	42/55 (76·3%)
Enterobacter spp. (n= 44)	ES cephalosporins	20/44 (45·4%)	6/20 (30·0%)	10/24 (41·6%)
	Carbapenems	9/ 44 (20·4%)	4/9 (44·4%)	12/35 (34·2%)
	MDR	22/44 (50·0%)	8/22 (36·3%)	8/22 (36·3%)
Gram-positive				
Coagulase negative staphylococci (n=150)	Methicillin	85/140 (60·7%)	23/85 (27·0%)	14/55 (25·4%)
	Vancomycin	0/138	-	36/138 (26·0%)
Staphylococcus aureus	Methicillin	43/114 (37·7%)	16/43(37·2%)	22/71 (30·9%)

Resistant vs. sensitive:

CFR almost the same despite app. treatment!!

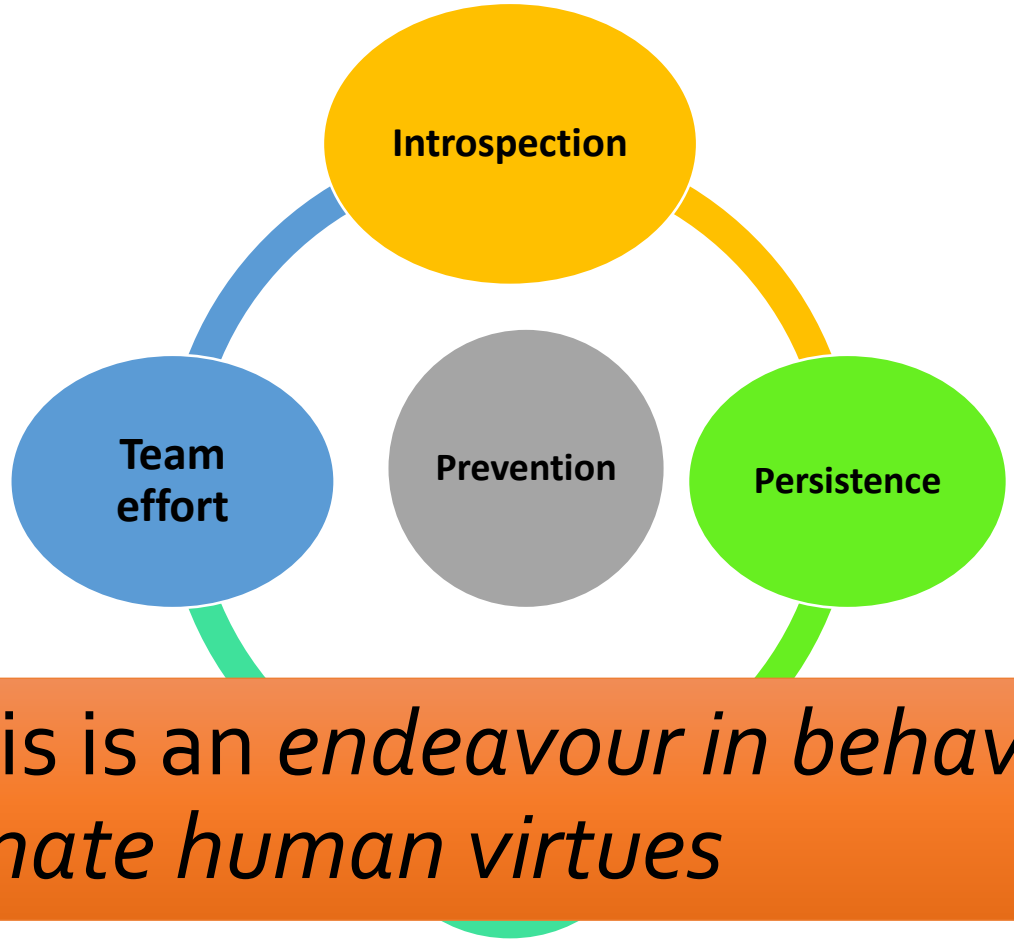
Prevention: CDC: 12 steps



CDC 2002

How do we deal with this situation?

- **PREVENTION**, is naturally the key



In essence, this is an *endeavour in behaviour change, bolstering innate human virtues*

Prevention: Simple ‘bundles’

- Rational admission policy
- Shortened NICU stay
- Curbing of ‘routines’
- Asepsis routines
- Aggressive enteral nutrition
- Rational antibiotic therapy
- Training of nurses

Agarwal 2007

Introspection

Prevention: Simple ‘bundles’

- Rational admission policy
- Shortened NICU stay
- Curbing of ‘routines’
- Asepsis routines
- Aggressive enteral nutrition
- Rational antibiotic therap
- Training of nurses

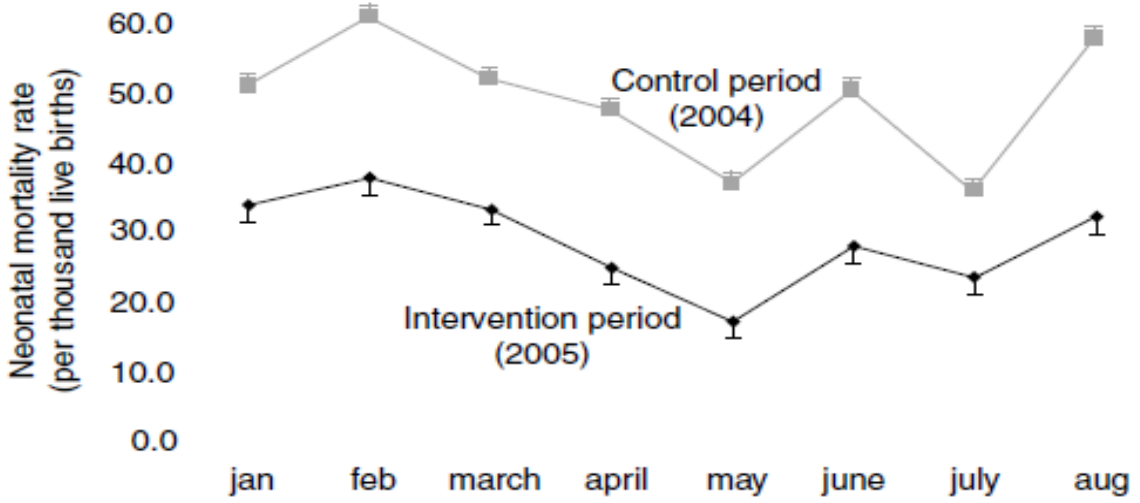


Figure 1 Trends in NMR (with standard error bars) during two time periods.

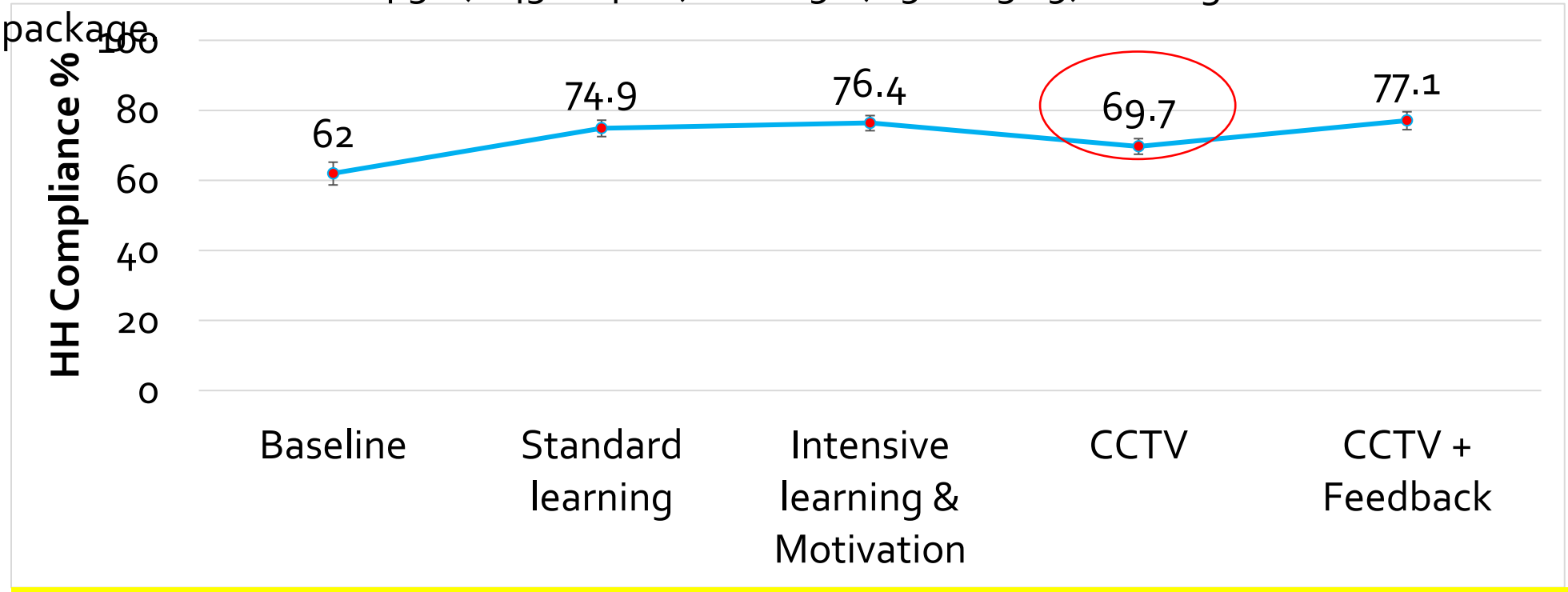
NMR reduced by 40%

Agarwal 2007

INTROSPECTION

Hand hygiene: compliance

- WHO-5 campaign of HH compliance : system change, training and education, observation and feedback, reminders in the hospital, and a hospital safety climate.
- A meta-analysis among HCPs, mean OR (95% credible interval) improvement compared with no intervention were 4.30 (0.43 to 46.6) and 6.51 (1.58 to 31.9) for single intervention and whole package

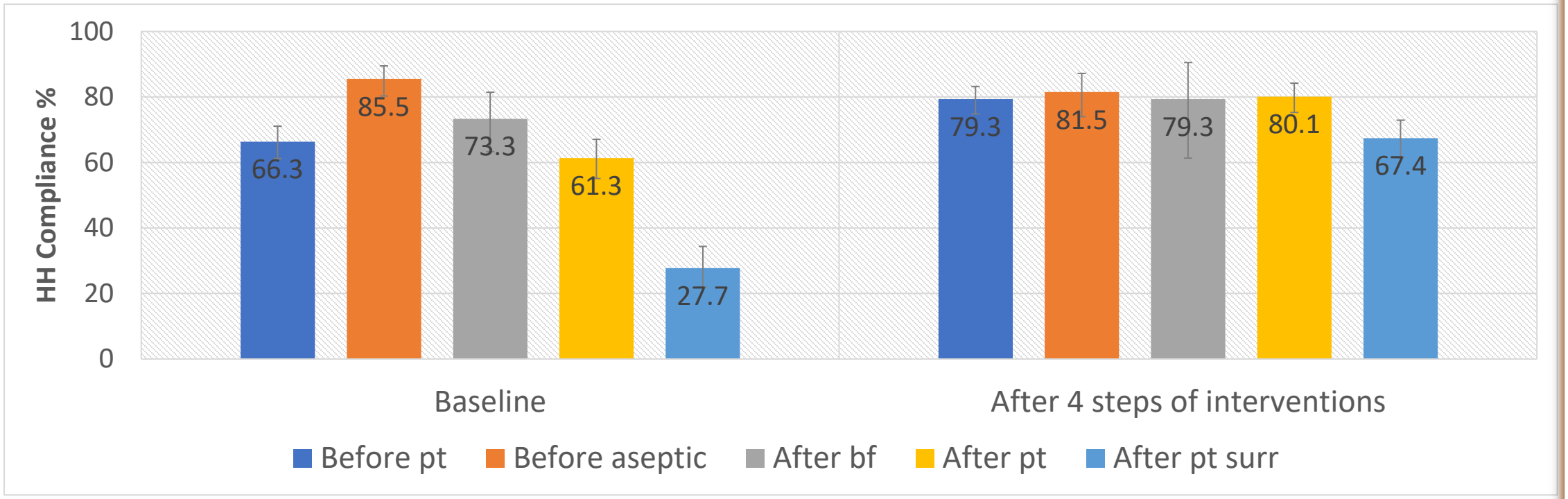


- Significant improvement in hand hygiene compliance of health-care providers with educational interventions
- Feedback remains an important modality for behaviour change besides monitoring (CCTV).

PERSISTENCE

Luangasanatip et al 2015, *Shridhar et al 2015*

Hand hygiene: compliance



- Also keep a watch at WHO's 5 moments; keep a deeper perspective
- Persist with continued training

PERSISTENCE

Shridhar et al 2015

Antimicrobial stewardship

1. Timely antibiotic management
2. Appropriate selection- Antibiotic policy
3. Appropriate administration and de-escalation
4. Availability of expertise at the point of care
5. Data monitoring and transparency

PATIENCE

Recent evidence: reduction in emergence of MDR-GNB by 51%

Antimicrobial stewardship (ASP)

C3-NICU

DEPARTMENT OF PEDIATRICS
ALL INDIA INSTITUTE OF MEDICAL SCIENCES

शरीरमाद्यं खलु धर्मसाधनम्

ANTIBIOTIC POLICY

ANTIBIOTIC FORMULARY AUTHORIZATION POLICY

PATIENCE

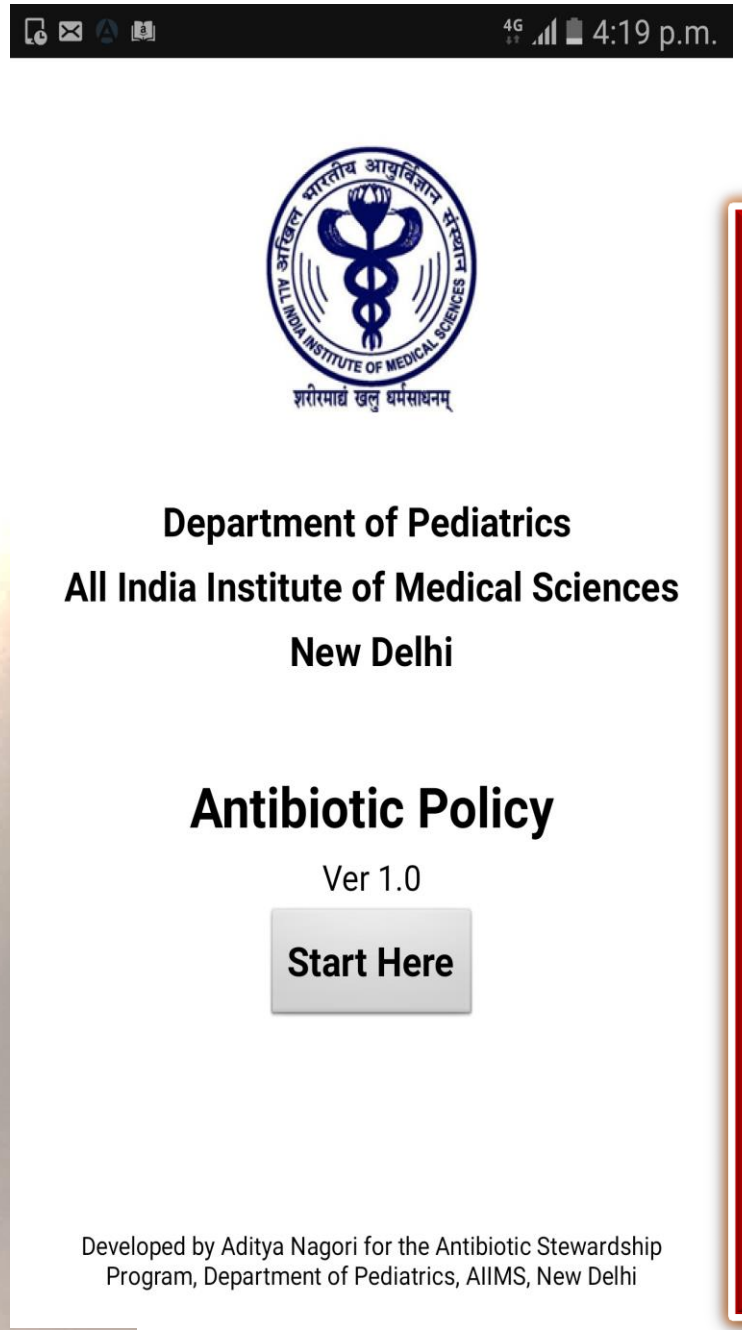
ASP

Department of Pediatrics

AIIMS, New Delhi

Antibiotic Formulary Authorization Policy

	Antibiotic	Authorization by
1.	Colistin	Unit Head + Head of Deptt.
2.	Tigecycline	Unit Head
3.	Aztreonam	Unit Head
4.	Ertapenem	Unit Head
5.	Vancomycin	Consultant on call/ round
6.	Teicoplanin	Consultant on call/ round
7.	Linezolid	Consultant on call/ round
8.	Meropenem	Consultant on call/ round
9.	Imipenem	Consultant on call/ round
10.	Cefoperazone-sulbactam	Consultant on call/ round
11.	Piperacillin-tazobactam	Consultant on call/ round
12.	Clindamycin	Consultant on call/ round
13.	Cefepime	Consultant on call/ round
14.	Ceftazidime	Consultant on call/ round
15.	Ceftriaxone	Senior Resident
16.	Cefotaxime	Senior Resident
17.	Ceftazidime	Senior Resident
18.	Amox-clavulanic acid	Senior Resident
19.	Aminoglycoside-gentamicin, amikacin	Senior Resident
20.	Ciprofloxacin	Senior Resident
21.	Ofloxacin	Senior Resident



PATIENCE

Key concepts

Prevention of MDR infection must be the cornerstone

Prevent infections (with *introspection and persistence*)	**Appropriate treatment (with *patience* and *team work*)**
• Simple 'bundles' • Hand hygiene	• Antibiotic policy • Antimicrobial stewardship • Accurate diagnosis • Use biomarkers wisely

ASP: Appropriate Treatment

ESBL+ GNB	**Carbapenems**
Carbapenem-resistant GNB	Ciproflox; Carbapenem + AG or ciproflox or colistin **Colistin**
XDR GNB	**Co-trimoxazole** **Chloramphenicol** Fosfomycin Tigecycilne

PATIENCE

ASP: accurate diagnosis- hematological

Table 1
Performance of hematological findings and a hematological scoring system in 298 neonates evaluated for sepsis during the first postnatal month[55]

Hematological Finding	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
↑ I:T ratio[a]	96	71	25	99
↓ or ↑ neutrophil count[a]	96	61	20	99
Immature:mature ratio ≥0.3	93	81	32	99
↑ immature neutrophil count[a]	63	69	17	95
↓ or ↑ white cell count[b]	44	92	36	94
Neutrophil degenerative changes ≥3+[c]	33	95	39	93

Poor PPV:
Not sure of infection!

PATIENCE

ASP: accurate diagnosis- CRP

	ANC* <5580/mm3	I/T * > 0.2	CRP > 1.0 mg/dL	WBC<5000/mm^3 I/T > 0.2 & CRP > 1.0 mg/dL
Sensitivity	48	90–100	70–93	100
Specificity	73	30– 78	78– 94	83
PPV	4	11– 51	7– 43	27

- Use adjunct tests to **RULE-OUT** sepsis!
- Do **NOT use** to 'rule-in' (**diagnose**) sepsis

High NPV!

PATIENCE

Upcoming strategies- what lies ahead

STOP antibiotics!

PCT: How best to use?

- 2 serial PCTs
  - 24 h after initial evaluation
  - 24-48 h after the first
- Both **negative**
- Clinical course not suggestive
- Cultures sterile

•*Stocker 2010- single centre study, n=121:* the standard group and the PCT group (absolute risk reduction 27%; odds ratio 0.27 (95% CI 0.12-0.62), p = 0.002).
•On average, PCT-guided decision-making resulted in a shortening of 22.4 h of antibiotic therapy
•*Stocker 2017- multicentric- RCT, n=1710:* For PCT group, the duration of therapy was reduced (intention to treat: 55·1 vs 65·0 h, p<0·0001; per protocol: 51·8 vs 64·0 h; p<0·0001)

H
O
P
E