

# Extended Spectrum $\beta$ - lactamases in the Neonatal Intensive Care Unit

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# Epidemiology of Nosocomial Infections in the Neonatal ICU

- Very high rates of nosocomial (hospital or healthcare-acquired) infections
- Gram positive organisms most common – ~ 50-60%
- Gram negative organisms
  - Increasing ~20%
  - More multidrug-resistant
- Fungal pathogens increasing- ~ 10%

# Risk Factors

- Intrinsic Immunologic Factors
  - Poor chemotaxis and ingestion by neutrophils
  - Low levels immunoglobulins
  - Low complement and fibrinogen levels
  - Decreased number of CD3, CD4, CD8, and NK cells
- Poor skin integrity
- Immature gastrointestinal development
- Extrinsic Factors
  - Instrumentation
    - Central venous catheters
    - Ventilators
  - Procedures
    - Surgery





# Case # 1

- 800 gram 28 week gestation
- Day of life (DOL) # 10
  - apnea and bradycardia
- DOL 12, blood culture (+) ESBL-producing *K. pneumoniae*
  - susceptible to piperacillin/tazobactam, cefoxitin, imipenem, meropenem, ciprofloxacin & amikacin
  - resistant to cefotaxime

## Case 2

- 535 gram 25 week twin
- DOL 116 developed catheter-related blood stream infection with ESBL-producing *K. pneumonia*
  - susceptible to piperacillin/tazobactam, ceftazidime, imipenem, meropenem, ciprofloxacin and amikacin
  - resistant to cefotaxime
- For next 5 days, she remained bacteremic:
  - abscess on right forearm
  - septic arthritis of right knee
  - osteomyelitis of right femur
  - All infectious collections drained and ESBL-producing *K. pneumonia* isolated
- Improved and completed 6 weeks of imipenem

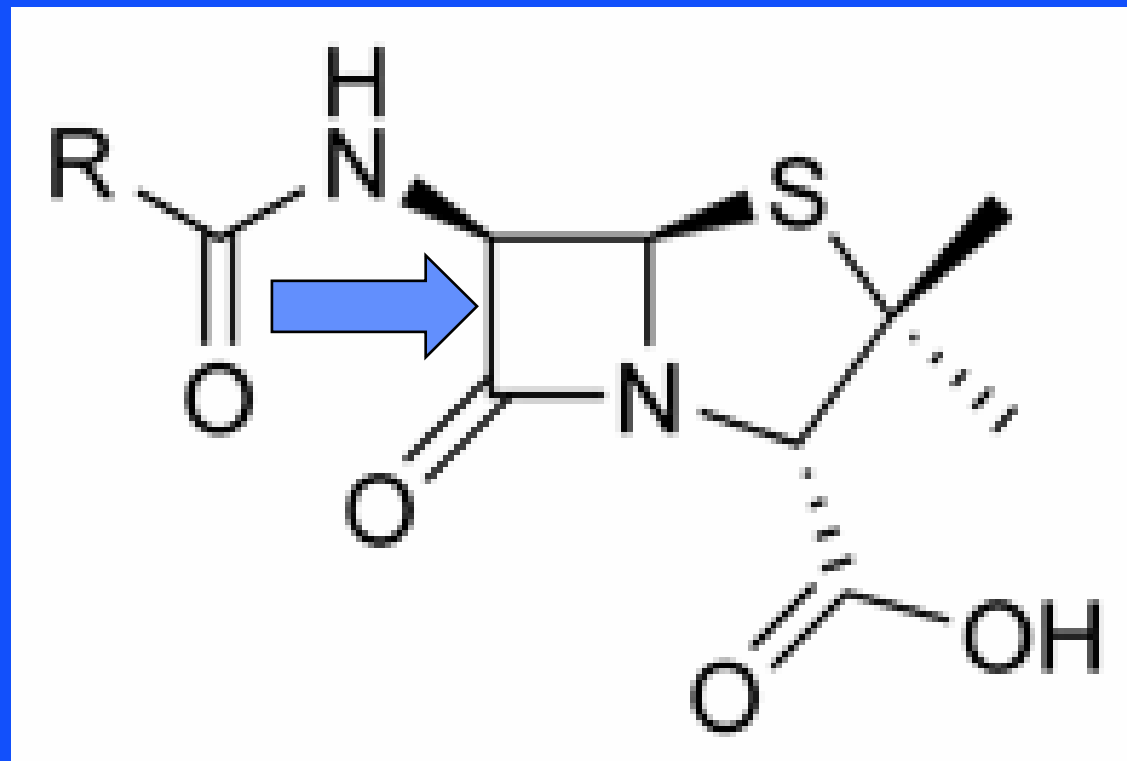
What is ESBL-  
production?

# $\beta$ -lactam antibiotics inhibit cell wall synthesis and bacterial cell division

**Table 1** Groups and examples of  $\beta$  lactam antimicrobial agents

$\beta$ lactam groups	Examples of antimicrobial agents
Penicillins	Penicillin G, penicillin
	Penicillinase resistant penicillins: methicillin, nafcillin, oxacillin, cloxacillin
	Aminopenicillins: ampicillin, amoxicillin
	Carboxypenicillins: carbenicillin, ticarcillin
	Ureidopenicillins: mezlocillin, piperacillin
Cephalosporins	First generation: cefazolin, cephalothin, cephalexin
	Second generation: cefuroxime, cefaclor, cefamandole, cefamycins (cefotetan, cefoxitin)
	Third generation: cefotaxime, ceftriaxone, cefpodoxime, ceftizoxime, cefoperazone, ceftazidime
	Fourth generation: cefepime, cefpirome
Carbapenems	Imipenem, meropenem, ertapenem
Monobactams	Aztreonam

$\beta$ -lactamase enzymes destroy  $\beta$ -lactam ring of  $\beta$ -lactam Antibiotics



# $\beta$ -lactamase Classification by Biochemical, Functional OR Molecular Structure

**Table 3** Evolution of functional classification of  $\beta$  lactamases

Year	Author	Basis of classification of $\beta$ lactamases
1968	Sawai et al	Used cephalosporins versus penicillins as substrates
1973	Richmond and Sykes	Expanded substrate profile and suggested five major groups (Ia-d, II, III, IV, V)
1976	Sykes and Matthew	Differentiated the plasmid mediated $\beta$ lactamases on the basis of isoelectric focusing
1981	Mitsuhashi and Inoue	Added the category "cefuroxime hydrolysing $\beta$ lactamase"
1989	Bush	Expanded further the substrate profile, added the reaction with EDTA, correlated between functional and molecular classification
1995	Bush, Jacoby, and Medeiros	Expanded the Bush scheme and used biochemical properties, molecular structure, and nucleotide sequence. Suggested classification into four groups (1-4)* on the basis of the spectrum of activity and other functional characteristics

\*Details in text and in table on [bmj.com](http://bmj.com)

# Extended Spectrum Beta-lactamases

- Plasmid encoded  $\beta$ -lactamase
- Hydrolyze 3<sup>rd</sup> generation cephalosporins
  - ceftazidime, cefotaxime
- Initially detected in *K. pneumoniae*
- Spread species to species
- Inhibition *in vitro* by beta-lactamase inhibitors
  - Can fail *in vivo*
- Treatment of choice is imipenem/ meropenem

# Phone call from Director of NICU to Hospital Epidemiologist

“We have just diagnosed three infants with *Klebsiella pneumoniae* bloodstream infections.

These strains are highly resistant to antibiotics. In fact, they are resistant to 3rd generation cephalosporins, aminoglycosides, and piperacillin-tazobactam.

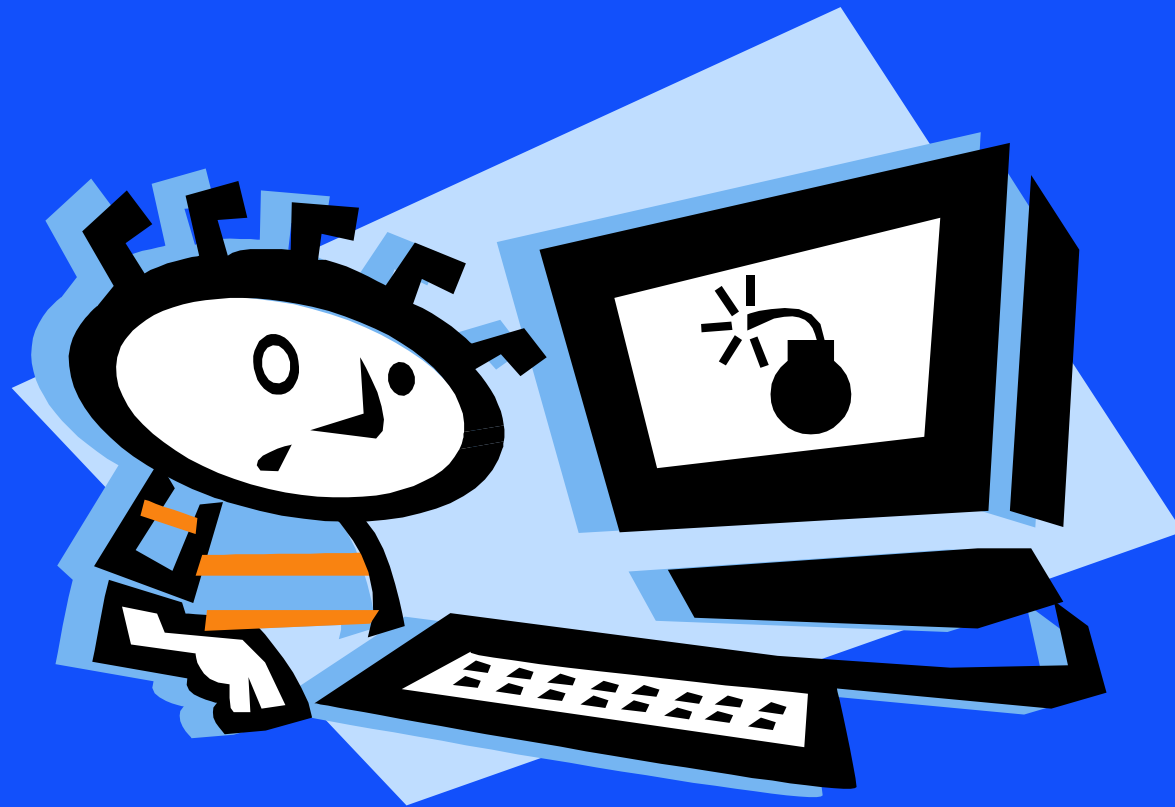
Do you think we are having a problem?”

YES!!!!

# Role of Hospital Epidemiologist

- Active surveillance of high risk patients for hospital-acquired infections
- Investigate potential outbreaks
- Prevent patient-to-patient transmission of potential pathogens
- Prevent transmission of pathogens to and from:
  - health care workers
  - visitors

# Descriptive Epidemiology of *K. pneumoniae* in the NICU



# Case Definition

- Infant in the NICU with (+) culture for ESBL *K. pneumoniae* isolated from any body site during the past year.
- Colonized and/ or infection
  - Colonization has same infection control implications as such infants serve as reservoirs of potential pathogens

# Create a Line Listing

- Name, medical record number, date of birth
- Date of admission and discharge
- Room location
- Co-morbid conditions
- Onset of infection
- Body site
- Procedures
- Medications
- PFGE clone



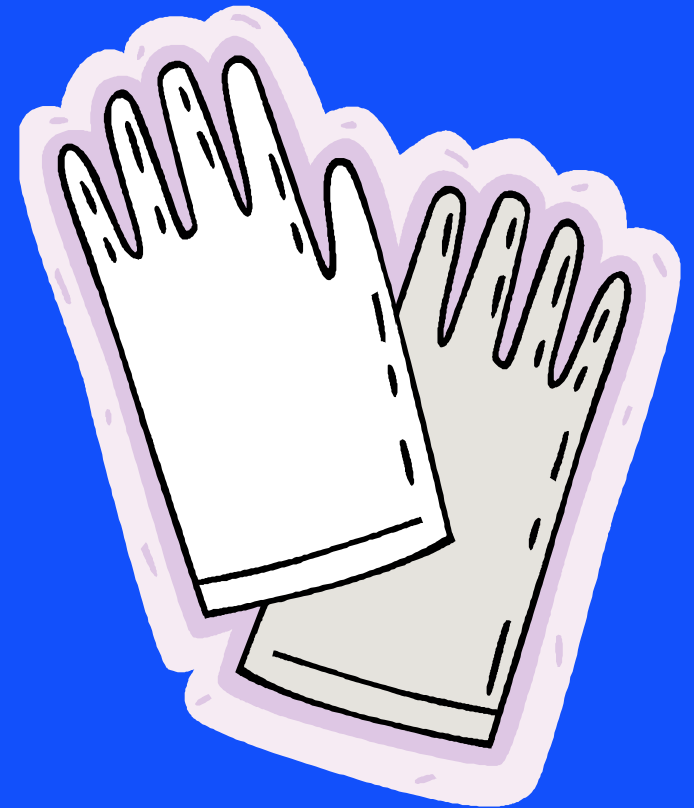
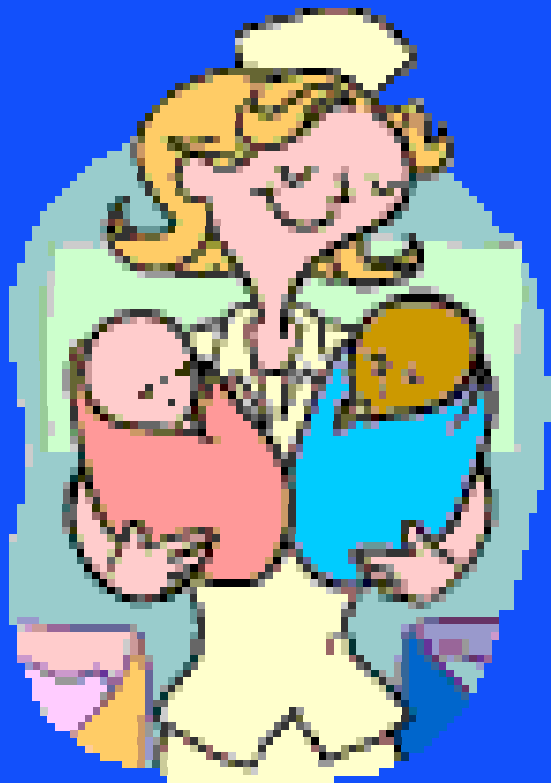
# Calculate Incidence

- ***Numerator:*** number of cases of infants infected or colonized with ESBL *K. pneumoniae*
- ***Denominator:*** 1000 patient- days per month

# Establish a Multi-Disciplinary Team

- Hospital epidemiology
- Unit staff: MDs and RNs
- Clinical microbiology laboratory
- Occupational Health Service
- Housekeeping
- Respiratory therapy
- Inform and update Chief of Department
- Risk Management

# Control Measures Implemented to Prevent Further Transmission

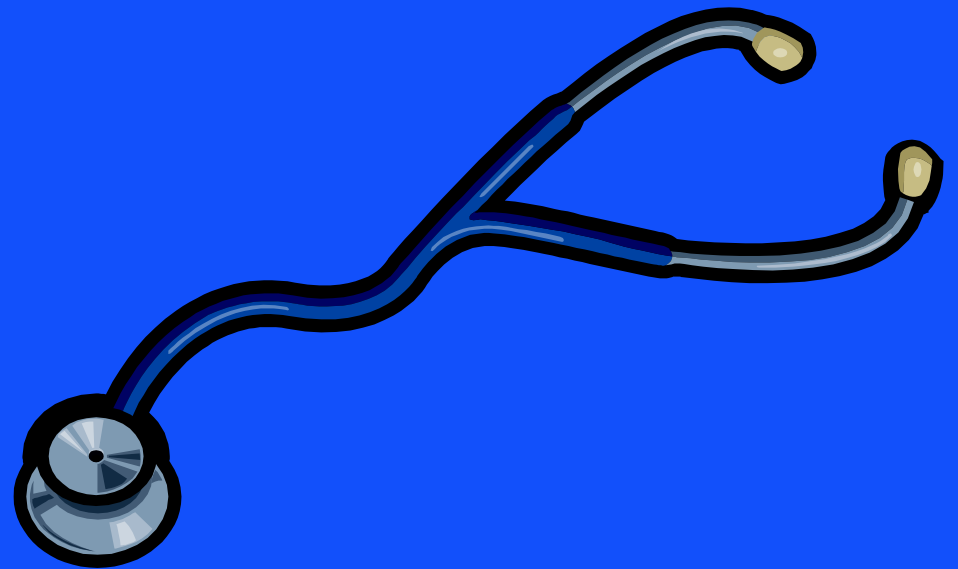


# Initial Control Measures

- **Contact Precautions:**
  - Infants infected/ colonized with ESBL *K. pneumoniae*
  - Workers gown and glove
- **Surveillance cultures:**
  - Identify other potential cases by culturing respiratory and gastrointestinal tracts of all babies in NICU.
- **Cohort:**
  - Known and newly detected cases together and assign designated nurses.

# Culture Environmental Sites

- Tap water
- Sink drains
- Liquid medications
- Respiratory therapy equipment
- Hand creams
- Water baths used to warm formula
- Designated stethoscopes



**These measures were  
not successful in  
preventing  
transmission.**

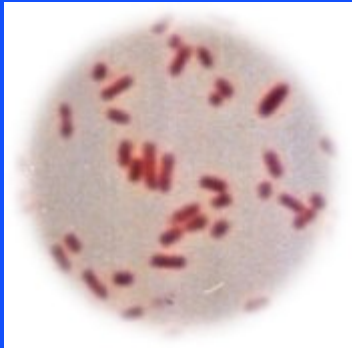
# Potential Routes of Transmission

- Repeat cultures from the environment
  - designated stethoscope (+) for ESBL *K. pneumoniae*
- Was patient-to-patient transmission occurring via the hands of healthcare workers?
  - Hands of 2 nurses (+) for ESBL *K. pneumoniae*
  - Both wore artificial nails

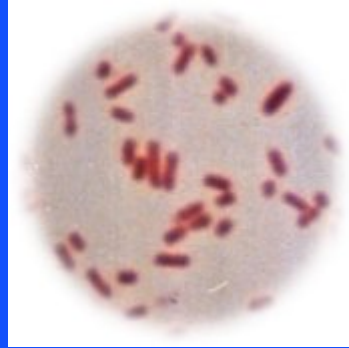
**Molecular typing was performed to determine if the strains from the hands of the healthcare workers were the same strain as found in the infants.**



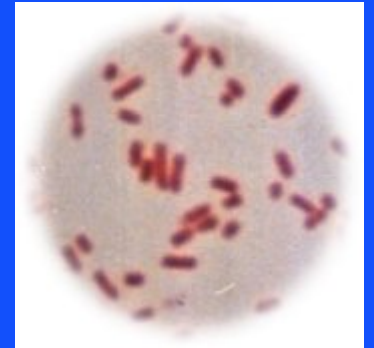
# ESBL *Klebsiella*



Patient 1



Patient 2



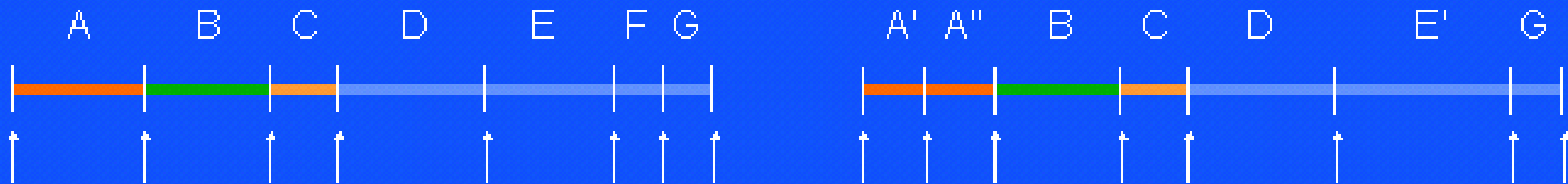
Patient 3

Are these related?

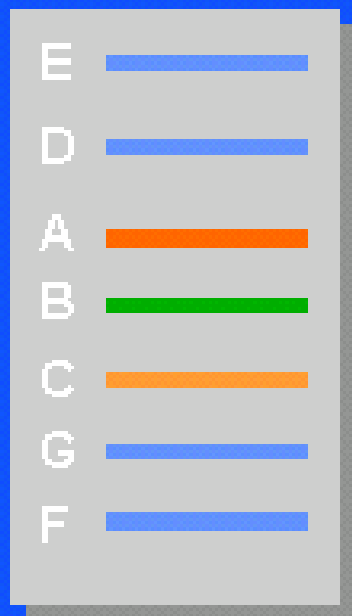
# Bacterial restriction endonuclease analysis

Isolate A

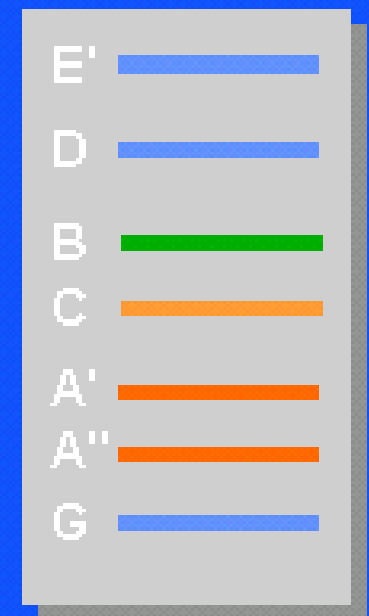
Isolate B



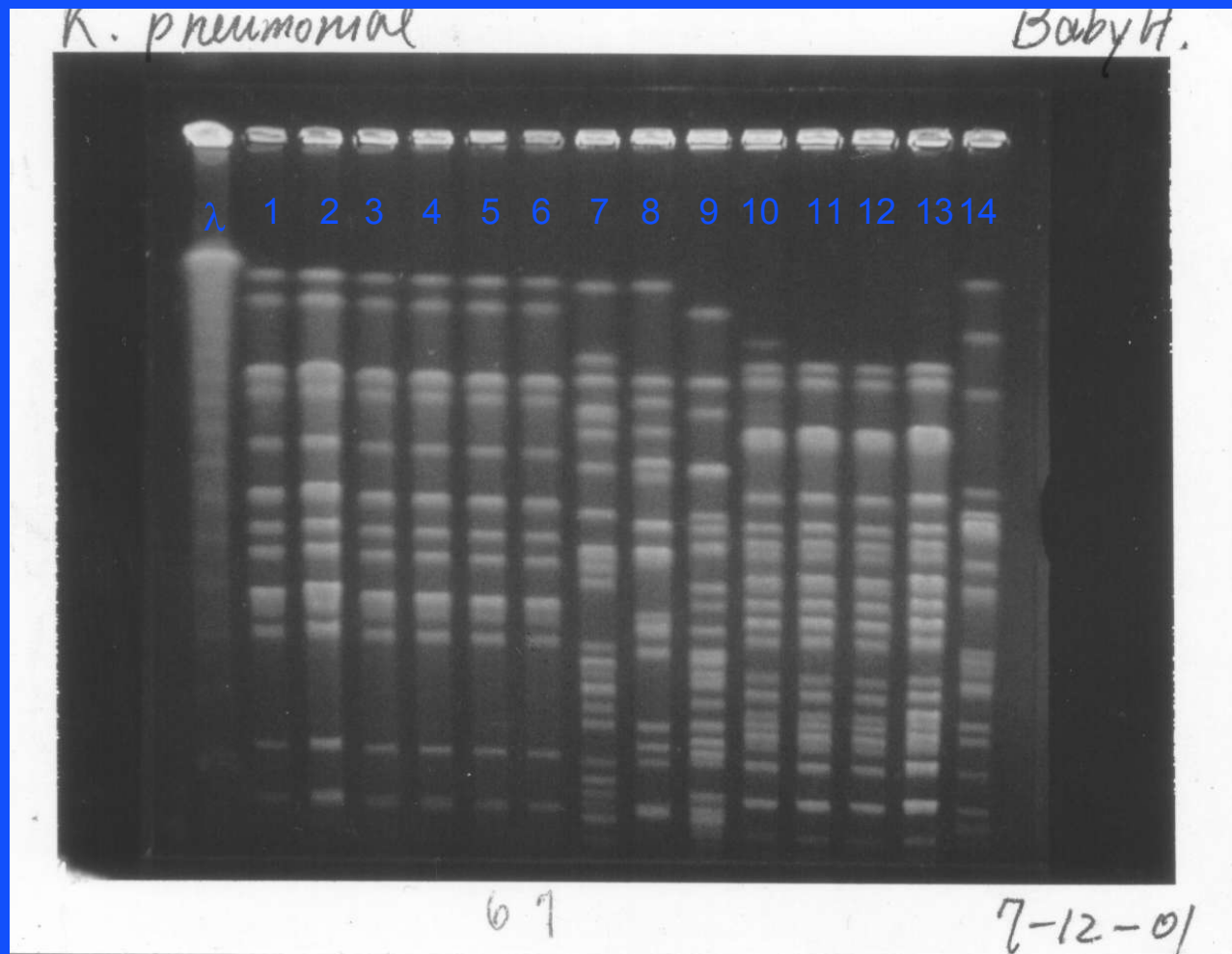
Digestion with *EcoRI*



← Agarose-gel electrophoresis →

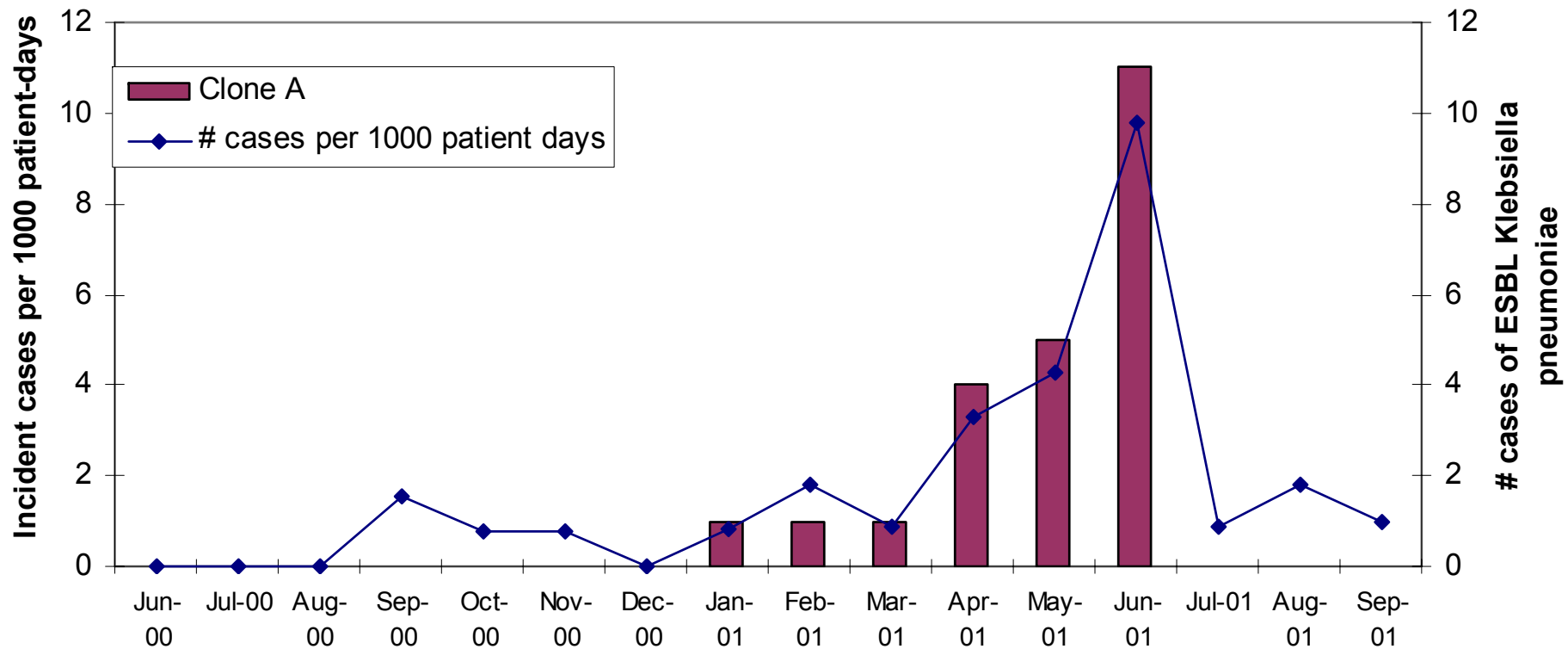


# PFGE of ESBL *K. pneumoniae*, NICU 2001



# Epi-Curve of ESBL *Klebsiella* in the NICU

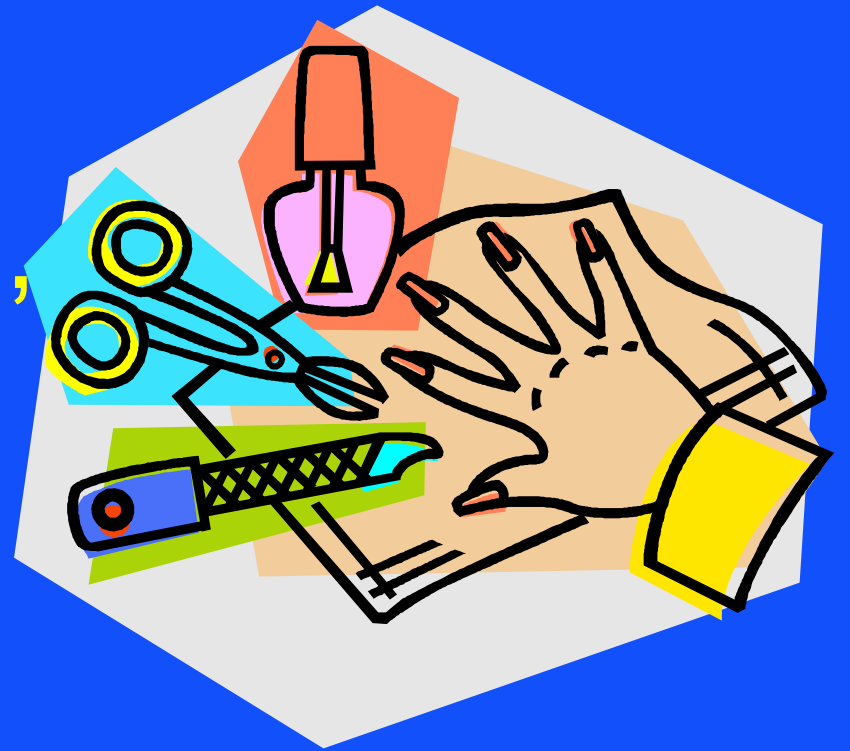
Figure 1: Incident cases of ESBL *Klebsiella pneumoniae* per 1000 patient-days in the NICU, June 2000-Sept 2001



# Case-Control Study Performed

- Risk factors for acquisition of ESBL *K. pneumoniae*
  - Cases: colonized or infected
  - Controls: hospitalized at the same time with (-) surveillance cultures
- Risk factors included:
  - Length of stay (OR 1.05 per day)
  - Care by Nurse A (OR 7.87)
    - (+) hand cultures
    - (+) artificial nails

Nurses furloughed,  
artificial nails removed,  
and repeat cultures  
were negative.



# Artificial Nails Banned from NYPH

- Only natural nails
- Nail polish is permitted
- Nothing adhered to nail
- No wraps, silks, appliqués, etc.

# Cost Analysis of Outbreak

- Laboratory costs for culturing
- Blocked beds = lost revenue
- Personnel time
- Increased length of stay
- \$342,000

