Educational Workshop

EW09: ESBL - how big is the threat?

arranged with ESGNI

(ESCMID Study Group for Nosocomial Infections)

Convenor: Christian Ruef (Zurich, CH)

Faculty: Patrice Nordmann (Paris, FR)
Hajo Grundmann (Bilthoven, NL)
Evelina Tacconelli (Rome, IT)
Christian Ruef (Zurich, CH)
Nordmann – Molecular basis of ESBLs

**Molecular bases of ESBLs**

- Hydrolysis of penicillins + expanded-spectrum β-lactams including most cephalosporins
- Inhibited by clavulanic acid, ticarcillin and sulbactam
- Do not hydrolyze cephalosporins or carbapenems (usually)
- Ambler class A β-lactamases
- Plasmid-encoded genes

**K. pneumoniae TEM-4**

Nordmann – Molecular basis of ESBLs

**ESBLs**

Classical

- **158D - SHV**
- **158S - TEM**

**Rares:** PER, VEB, BES, PPO GES, TLA, MGE...

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**The old story... the clavulanic-acid inhibited ESBLs (SHV, TEM)**

- **Epidemiology**
  - 1980-2000s
  - Nonmarket source
  - Worldwide
- **Prevalence**
  - *Escherichia coli, Salmonella spp.*
- **Risk factors**
  - ICU
  - Urinary, blood culture, surgery
  - Long-term hospitalization
  - β-Lactams, fluoroquinolones

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**Tn3-type transposon harboring _blaTEM-like_ genes**
Nordmann – Molecular basis of ESBLs

**IS26-mediated mobilization of blaTEM**  
(originating from Klebsiella pneumoniae)

**Rare to more or less frequent ESBLs**

VEN, TLA, GES, PER, BES....

**E. coli isolate producing VEB-1**
Nordmann – Molecular basis of ESBLs

E. coli isolate producing VEB-1

- First reported in France in E. coli from a Vietnamese patient (Hour et al., AAC 1999)
- Highest identity with ESBL-1 (38%)
- Equally inhibited by clavulanic acid, sulbactam, tazobactam, but also by moxalactam, imipenem and cefoxitin
- Then identified in many other enterobacterial species, Pseudomonas and Acinetobacter
- Widespread in Vietnam, Thailand and Korea in Enterobacteriaceae

The bla_{VEB1} gene is located in a class 1 integron

bla\_{VEB1}

Integron-, transposon- and plasmid-associated bla_{VEB-1}
Nordmann – Molecular basis of ESBLs

*P. aeruginosa* producing PER-1

**Spread of PER-1**

1) PER-1: first identified in a *P. aeruginosa* isolate in France from a Turkish patient (Nordmann et al., AAC 1993)

2) Widespread in Turkey, Italy, South Korea in *Pseudomonas*, Acinetobacter, and Enterobacteriaceae

3) Rarely identified in *E. coli*

**Genetic environment of bla_{PER-1}**

- Two different IS elements (63% amino acid identity at the TmpA level)
- Both belong to the IS4 family
- Similar inverted repeat sequences

Fondel et al., AAC 2003, 49:1708
Nordmann – Molecular basis of ESBLs

**TLA-1 in E. coli**
- Less than 50% amino-acid identity with other β-lactamases
- Plasmid-mediated
- Only identified in Mexico City
- Source of acquisition: unknown

**GES-1, GES-2, GES-3, GES-4**
- GES-2: E. coli in Thessaloniki from a Greek patient 1999
- GES-3, GES-4, GES-5: as a gene cassette inside a class 1 integron

**GES-1**
- First identified in K. pneumoniae (French Guyana) (Porel et al., AAC 2000)
- β-lactamase as a gene cassette inside a class 1 integron
- Then, identification in P. aeruginosa (France), in a different integron (Dubre et al., AAC 2002)
Nordmann – Molecular basis of ESBLs

The emerging ESBLs…

…community-acquired

Clovulanic-acid inhibited ESBLs are rising...

Prevalence of ESBL producers
(hospital Bicêtre, 1997-2005)

- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005

Years

Clovulanic-acid inhibited ESBL producers are different...

Hospital Bicêtre
Nordmann – Molecular basis of ESBLs

Species distribution in hospitals in Paris

CTX-Ms: cefotaxime and ceftazidime hydrolysis

The rising star: CTX-M-15
Nordmann – Molecular basis of ESBLs

The plasmid-mediated CTX-Ms

[Diagram showing CTX-Ms]

Adapted from Maselka et al., Curr 2008

Plasmid-mediated CTX-Ms: the origin

Kluyvera ascorbata

[Image of Kluyvera ascorbata]

Hennorah et al., AAC 2007

Plasmid-mediated CTX-Ms: the origin

[Diagram showing Kluyvera ascorbata]

Adapted from Masselka et al. Curr 2008
Nordmann – Molecular basis of ESBLs

**The insertion sequence ISEcpI and blaCTX-M**

ISEcpI responsible for mobilization and expression of β-lactamase genes by transposition using imperfect right inverted repeats

*Parid et al., AAC 2003,173-1739*

*Parid et al., AAC 2005,49-447*

**Genetic structures for blaCTX-M acquisition**

ISEcpI

CTX-M of different groups

**sul-type integrons**

- CTX-M-2 and CTX-M-9
- Prophage-related elements (CTX-M-10-CTX-M-1 group)

**Spread of ESBL genes**

- ICU
- Long term hospitalization
- Community

- E. coli
- Klebsiella
- Enterobacter sp.
Nordmann – Molecular basis of ESBLs

Spread of ESBL genes

Mobile elements

Klebsiella, Enterobacter sp.

ESBLs of a novel type: the KPC enzymes

- KPC-1
- >90% aa identity with Smp-1
- 44% with NMC-A and SME-1
- plasmid encoded (50 kDa)
- Imipenem resistance/ decreased susceptibility obtained by cleavage acid

Genetic elements involved in mobilization of ESBL genes

- Transposons for blaKPC
- IS1086 element for blaKPC
- Class 1 integrons for blaKPC, blaIMP
- Peculiar composite transposons for blaKPC-1
- IS26 transposons for blaKPC genes
- CRI element (sul1-type integrons) and phage-associated elements for some blaKPC genes
- Peculiar transposon for blaKPC genes
Nordmann – Molecular basis of ESBLs

Gene transfer

Adapted from Tenover, Clin Micro Dis. 2001; 9:5105

ESBL genes

Spread of ESBLs in clinically-significant Gram negatives

<table>
<thead>
<tr>
<th></th>
<th>Enterobacteriaceae</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>A. baumannii</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>SHV</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>CTX-M</td>
<td>+</td>
<td>+++</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>SHV</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>GES</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Take home message

- Increasing diversity of ESBL genes acquisition and dissemination are identified.
- Genomic plasticity at the origin of ESBL gene diffusion – increasing spread.
- Searching for the reservoirs
  - Mobile elements
  - Resistance genes
ESBLs
Incidence, Prevalence & Mode of Transmission

Hajo Grundmann
National Institute for Public Health and the Environment, Bilthoven
Rijksuniversiteit Groningen, NL

Epidemiology (of ESBLs)

- Two principal measures of disease occurrence in a population
  - Incidence
  - Prevalence

Incidence

no of new cases
Person time at risk during the entire investigation
Grundmann - Epidemiology

Prevalence

no of cases

| no of all individuals who were part of the population at the time of investigation |

Epidemiology of ESBLs

- Two principal measures of disease occurrence in a population
  - Incidence
  - Prevalence
- Numerator
- Denominator

Numerator

- Case definition in AMR surveillance?
- Two necessary criteria
  1. Person suffering from infection
  2. Caused by ESBL-producing organism
Grundmann - Epidemiology

Denominator

- Population under study
  - Hospital
  - Community

Incidence

*E. coli* Proportion 3rd Cephalosporin resistance in Europe
Proportions and cumulative incidence in Europe: *E. coli* 3rd gen ceph-resistance

**Third gen. cephalosporin resistance, proportion vs incidence in BSIs**

- Proportion Resistance
- N resistant/100000 patient days

**Proportions and cumulative incidence in Europe: MRSA**

**Incidence of BSI caused by 3rd gen ceph-resistant *E.coli* in 13 European hospitals**

<table>
<thead>
<tr>
<th>Country</th>
<th>Patient days at risk</th>
<th>12 month observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT (2137)</td>
<td>65,738</td>
<td></td>
</tr>
<tr>
<td>BE (856)</td>
<td>29,079</td>
<td></td>
</tr>
<tr>
<td>DE (1324)</td>
<td>39,125</td>
<td></td>
</tr>
<tr>
<td>GR (946)</td>
<td>29,363</td>
<td></td>
</tr>
<tr>
<td>HR (1724)</td>
<td>47,952</td>
<td></td>
</tr>
<tr>
<td>IE (819)</td>
<td>23,816</td>
<td></td>
</tr>
<tr>
<td>IT (912)</td>
<td>29,215</td>
<td></td>
</tr>
<tr>
<td>LV (1029)</td>
<td>30,700</td>
<td></td>
</tr>
<tr>
<td>MT (835)</td>
<td>25,248</td>
<td></td>
</tr>
<tr>
<td>RO (1109)</td>
<td>42,766</td>
<td></td>
</tr>
<tr>
<td>SC (877)</td>
<td>25,815</td>
<td></td>
</tr>
<tr>
<td>SI (2344)</td>
<td>61,435</td>
<td></td>
</tr>
<tr>
<td>UK (1218)</td>
<td>29,263</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4,791,550</td>
<td></td>
</tr>
</tbody>
</table>
Grundmann - Epidemiology

Incidence of BSI caused by 3rd gen ceph-resistant E.coli in 13 European hospitals

Prop (%) 3rd gen ceph-resistant among E. coli BSI in 13 European hospitals

Comparison 13 European hospitals vs. EARSS data
Grundmann - Epidemiology

**Age distribution among patients with E. coli blood stream infections (susceptible vs. 3rd gen. ceph-resistant)**

![Bar chart showing age distribution with susceptible and resistant bars.]

**Combined resistance in E. coli isolates from blood stream infections**

<table>
<thead>
<tr>
<th>g3cep</th>
<th>FO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>S</td>
<td>83%</td>
<td>17%</td>
</tr>
<tr>
<td>R</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>Total</td>
<td>1015</td>
<td>312</td>
</tr>
</tbody>
</table>

**Prevalence**
Prevalence

- In case of ESBL-producing organisms
  - does not denote a disease experience
  - is merely an estimate of the number of individuals carrying ESBL-producers in a defined population

Prevalence

- Liaoning Province, China
  - community sample of elderly >65
  - n=270
  - 7%
  - Tian SF, 2008

- India
  - carriage rate estimate
  - 10%
  - Hawkey P, 2009

Prevalence

- Saudi Arabia
  - healthy carriage
  - only E. coli and K. pneumoniae
  - n=426
  - 13.1%
  - Kadar A, 2007

- Israel
  - carriage on hospital admission
  - n=167
  - 13%
  - after two weeks of hosp. stay 33%
Prevalence

- Sweden
  - patients with abdominal infections
  - n=129
  - 10.9% (antibiotic exposure)
  - on admission 5.4%
    
    Tärnberg M, 2008

- Sweden
  - carriage in travellers (n=48)
  - returning form vacation (n=40, 2 weeks median stay)
  - median age 39 years
  - 36%

  Tängdén Th, 2008

Mode of transmission

- Family contacts in Spain
  - UTI index patients 66% carriage
  - household members 27%
  - non-household relatives 16%
  - non relatives 7%
  - eating out during previous 15 days (OR=0.2, 0.06 - 0.6)

  Rodríguez-Baño J, 2008

- Family contacts in Spain
  - carriage in index patients 70% (n=40)
  - carriage in household members 17% (n=64)
  - 66% had a PFGE pattern indistinguishable from index case

  Valverde A, 2008
Grundmann - Epidemiology

ESBL at Ramón y Cajal University Hospital (1988-2000) Madrid, Spain

Patient and patient/clones per year

……and how to control it?

Red Queen to Alice: “Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!”

Thanks

EARSS-MT

Marlieke de Kraker
Jos Monen
Hakan Hanberger
Otto Cars
Fernando Baquero
Raphael Canton
Impact on patient outcome

Evelina Tacconelli

Div. Infectious Diseases
Università Cattolica Sacro Cuore
Roma, Italy

ESBL - how big is the threat?

Impact on patient outcome

Multidrug resistant bacteria and mortality

Meta-analyses have documented that bloodstream infections caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and multidrug-resistant *Acinetobacter baumannii* are associated significantly with mortality

Cosgrove, CID, 2003; Diaz Granados, CID, 2005; Tacconelli, J hosp infect 2006; Falagas, Crit Care, 2006

- It is not universally accepted that ESBL production per se is responsible for adverse outcomes in invasive infections
- Data on the specific impact of ESBL production on outcomes in Enterobacteriaceae infections are scarce
- The lack of consensus is likely due in large part to small sample sizes and a resultant lack of sufficient statistical power to demonstrate an effect
Tacconelli – Impact on patient outcome

Limits of outcome analysis
Antibiotic-resistant infections

- Study design (mainly retrospective, case-control, cohort)
- Erroneous selection of the control group, matching criteria
- Heterogeneous grouping of antimicrobial classes
- Lack of analysis of multiple resistance patterns

Harris, CID, 2001, 2002
Kaye, ICHE, 2005;
McGregor, J clin epidemiol, 2005;
Tacconelli, ICHE, 2006

Limited controlling for confounding

- Risk attributable to comorbidity
- Context where data are gathered (outbreaks or endemic situations)
- Special patients populations
- Infection versus colonization
- Length of hospitalization
- Site of acquisition

Limits of outcome analysis
Antibiotic-resistant infections due to ESBL-producing bacteria

- Mainly retrospective cohorts
- Small sample size
- Lack of adjustment of the OR for mortality by multivariate analysis
- Subgroup analysis by type of micro-organisms missing
- Heterogeneous definitions of effective therapy and delay of therapy
- Mixed population
- Different length of follow up
Road map
Where is the evidence?

- Mortality and delay in effective therapy associated with ESBL infections
- Efficacy differences among treatment agents

Mortality and delay in effective therapy associated with ESBL bacteraemia

- A literature search was performed through to 30 April 2006
- Search strategy: 'bacteremia or bloodstream' and 'ESBL or extended-spectrum beta-lactamase'
- No language restrictions
- Subgroup meta-analyses geographical area age variation

Schwaber, JAC, 2007

Mortality and delay in effective therapy associated with ESBL bacteraemia

| Reference | ESBL agents | ESBL non-ESBL | Mortality (%) | Delay in effective therapy
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Schwaber</td>
<td>39 30 198</td>
<td>25 18 60</td>
<td>7</td>
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<tr>
<td>Dingle</td>
<td>35 24 133</td>
<td>15 13 54</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Martini</td>
<td>35 24 133</td>
<td>15 13 54</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fantini</td>
<td>35 24 133</td>
<td>15 13 54</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Corsi</td>
<td>35 24 133</td>
<td>15 13 54</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Abate</td>
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<td>3</td>
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Schwaber, JAC, 2007
Mortality and delay in effective therapy associated with ESBL bacteraemia

- The meta-analysis demonstrated an almost 2-fold increase in mortality associated with ESBL production among patients with Enterobacteriaceae bloodstream infection.
- The study could not prove that the increased mortality is directly attributable to ESBL production, as almost all existing studies do not provide adjusted results.
- The study showed a 5-fold increase in the proportion of patients with delayed institution of effective therapy in the ESBL group.
New evidence ..after March 2006

Mortality and delay in effective therapy associated with ESBL bacteraemia

**E. coli**

<table>
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<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
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<tr>
<td>ESBL producer</td>
<td>2.91 (1.20-6.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age*</td>
<td>1.07 (1.04-1.10)</td>
<td>0.027</td>
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<td>Sex</td>
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<td>0.597</td>
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<tr>
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</tr>
<tr>
<td>ICU</td>
<td>4.28 (1.25-14.39)</td>
<td>0.018</td>
</tr>
<tr>
<td>Time of infection</td>
<td>0.82 (0.47-1.42)</td>
<td>0.497</td>
</tr>
<tr>
<td>Bile</td>
<td>1.25 (0.39-4.28)</td>
<td>0.745</td>
</tr>
<tr>
<td>Other</td>
<td>2.86 (1.03-7.87)</td>
<td>0.042</td>
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*Where k = 3, p-value = 0.018

Mortality and delay in effective therapy associated with ESBL bacteraemia

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Table 2. Mortality and delay in effective therapy associated with ESBL bacteraemia

**E. coli**

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</tr>
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*Where k = 3, p-value = 0.018
Mortality and delay in effective therapy associated with ESBL bacteraemia E. coli. Haematological patients

Table 2: Analysis of factors associated with death at 30days after admission in 17 patients with nosocomial Klebsiella pneumoniae bacteraemia (determined by E. coli, K. pneumoniae).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.41 (0.99–2.00)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Antimicrobial therapy</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Diabetic mellitus</td>
<td>0.96 (0.61–1.56)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Postoperative state</td>
<td>1.00 (1.00–1.00)</td>
</tr>
</tbody>
</table>

Mortality and delay in effective therapy associated with ESBL bacteraemia K. pneumoniae

- Retrospective case—control study
- 17 cases
- No association with a worse clinical outcome compared to ESBL-negative controls

Mestdagh-Deurne, Infect Dis, 2009
Mortality associated with ESBL infections

NO

Mortality and delay in effective therapy associated with ESBL bacteraemia

YES

Tumbarello, AAC, 2009

Mortality associated with ESBL wound and urinary tract infections

NO
Mortality and delay in effective therapy associated with ESBL infections

<table>
<thead>
<tr>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
</tr>
</tbody>
</table>

Efficacy differences among treatment agents

Infections due to ESBL-producing bacteria

Treatment

- Infections due to ESBL-producing organisms present a major therapeutic dilemma as the choice of antibiotics is extremely limited

- Carbapenems (imipenem/cilastatin, meropenem, ertapenem, doripenem) are considered 1st line choice for treatment of serious ESBL infections
Tacconelli – Impact on patient outcome

**Infections due to ESBL-producing bacteria**

**Treatment**
- Quinolones are valid alternative for UTIs if there is no in vitro resistance to quinolones
- *In vitro* resistance of ESBL producers to quinolones is increasing
- Possible synergy with ciprofloxacin and imipenem, or cefotaxime/sulbactam, but no publications on clinical use of these combinations

**Infections due to ESBL-producing bacteria**

*"New"* treatments
- Colistin and polymyxin B are being used more frequently to treat serious infection, sometimes as monotherapy or in combination with other antibiotics.
- Clinical experience is broadening
- Tigecycline had good *in vitro* activity against most ESBL-producing Enterobacteriaceae
  - **Main limits**
  - Resistance already described in vivo
  - Low excretion of the compound in the urine

**ESBL and patient outcome**

**Conclusions**
- Based on existing evidence, prompt initiation of appropriate antimicrobial treatment is essential in patients with bacteraemia due to ESBL-producing bacteria
- Multi-institutional researches are required to define the best treatment according to study population, type of infection, ICU stay, treatment regimens, and species and type of ESBL causing infection.
ESBL and patient outcome

Conclusions

- Benchmark guidelines for researches focused on outcomes of antimicrobial resistant infections should be elaborated

- Funds to develop diagnostic and new therapeutic strategies are needed
ESBL

Infection control measures: same as with MRSA or different?

Christian Ruef, MD
University Hospital of Zurich
Switzerland

Key issues
- Goals of infection control measures
- Biology of ESBL: colonization
- Evidence for individual infection control measures
- Unresolved issues
- Conclusions

Goals of infection control measures
- Prevention of transmission between individual patients (endemic situation)
- Interruption of ongoing transmission (epidemic situation)
Biology of ESBL colonization — comparison with MRSA

<table>
<thead>
<tr>
<th></th>
<th>MRSA</th>
<th>ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site</td>
<td>Nares</td>
<td>Intestinal tract</td>
</tr>
<tr>
<td>Secondary site(s)</td>
<td>Skin, wounds</td>
<td>Urine, wounds</td>
</tr>
<tr>
<td>Other locations</td>
<td>Lower respiratory tract</td>
<td>Skin, lower respiratory tract</td>
</tr>
<tr>
<td>Occasionally</td>
<td>Urine, intestinal tract</td>
<td>Nares</td>
</tr>
</tbody>
</table>

Anatomical distribution of colonization: S. aureus versus ESBL

<table>
<thead>
<tr>
<th></th>
<th>ESBL positive samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>66.6%</td>
</tr>
<tr>
<td>Lung</td>
<td>42.6%</td>
</tr>
<tr>
<td>Wounds</td>
<td>39.7%</td>
</tr>
<tr>
<td>Urine</td>
<td>36.5%</td>
</tr>
<tr>
<td>Nares</td>
<td>38.7%</td>
</tr>
<tr>
<td>Groin</td>
<td>38.7%</td>
</tr>
<tr>
<td>Axilla</td>
<td>36.5%</td>
</tr>
</tbody>
</table>

Evidence for individual infection control measures
Ruef – Infection control measures

Possible infection control measures
- Contact isolation
- Restriction of antibiotic use
- Screening of patients (surveillance cultures)
  - On admission
  - Regular intervals
- Screening of healthcare workers
- Decolonization of patients
- Preemptive decontamination (SDD)

Effect of contact isolation on prevention of ESBL transmission – example 1
- 1000 bed teaching hospital in Barcelona: detection of 3 cases of ESBL-Klebsiella in ICU
  
  Contact isolation measures (June 93):
  - gloves
  - gowns
  - teaching: hand washing

  Peña C et al. AAC 1998

Effect of contact isolation on prevention of ESBL transmission – example 1
- Contact isolation without noticeable effect

  September 93: Restricted use of
  - Ceftriaxone
  - Cefotaxime
  - Ceftazidime

  Peña C et al. AAC 1998
Ruef – Infection control measures

Effect of antibiotic restriction on prevention of ESBL transmission – example 1

- No obvious effect of antibiotic restriction
  - Oct/Nov.: weekly surveillance screening (rectal swabs)
  - Detection of subclinical reservoir = colonized patients

Peña C et al. AAC 1998

Effect of contact isolation on prevention of ESBL transmission – example 1

- Lag time: 12 months

Peña C et al. AAC 1998

Conclusions from example 1

- Contact isolation without obvious impact
- Restriction of cephalosporine use without short term impact
- Surveillance screening detects reservoir of subclinical cases
- It takes 1 year to get the outbreak under control (more or less)
Effect of contact isolation on prevention of ESBL transmission – example 2

- 1200 bed hospital in Paris, France

Program to minimize ESBL dissemination (February 1992):
- Contact isolation
- Marking charts, doors, etc.
- Gloves, gowns
- Handwashing with antiseptic soap
- Reporting positivity (transfer)
- SDD during first year
- Surveillance cultures
- Admission
- Weekly

ESBL acquisition

During 1992
- 121 patients with ESBL
- Most acquired cases in ICUs

Observation of compliance during patient care (Jan 93)

Compliance rate, January 1993 (%)

Lucet J-C. CID 1999
Ruef – Infection control measures

Effect of contact isolation on prevention of ESBL transmission – example 2

- Enforced teaching
  - Importance and technique of hand washing; booklet
  - Channeling phone calls from relatives away from busy nursing hours
  - Establishing lists of materials needed for dressing changes, etc.
  - Emphasis on compliance of non-ICU staff: surgeons, physiotherapy, radiology

Lucet J-C. CID 1999

Effect of contact isolation on prevention of ESBL transmission – example 2

Impact of enforced teaching on compliance rate

<table>
<thead>
<tr>
<th></th>
<th>Hand washing before</th>
<th>Hand washing after</th>
<th>Gown worn</th>
<th>Gloves worn</th>
<th>Correct around interruption*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>57</td>
<td>71</td>
<td>79.5</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>1993</td>
<td>70</td>
<td>92.5</td>
<td>80.6</td>
<td>87.1</td>
<td>80</td>
</tr>
<tr>
<td>1994</td>
<td>70</td>
<td>90</td>
<td>90.6</td>
<td>87.1</td>
<td>90</td>
</tr>
<tr>
<td>1995</td>
<td>57</td>
<td>71</td>
<td>79.5</td>
<td>70</td>
<td>71</td>
</tr>
</tbody>
</table>

*Significantly less interruptions during 1994

Lucet J-C. CID 1999

Effect of contact isolation on prevention of ESBL transmission – example 2

Annual incidence of ESBL acquisition

- Start infection control
- Enhanced compliance

Lucet J-C. CID 1999
Ruef – Infection control measures

Effect of contact isolation on prevention of ESBL transmission – example 3

- 858-bed university hospital in Brussels
  - 31 mixed medical-surgical ICU beds

Increase in nosocomial ESBL cases

Promotion of routine infection control measures

Laurent C. ICHE 2008

Effect of contact isolation on prevention of ESBL transmission – example 3

- Routine infection control strategies
  - Surveillance of intestinal colonization
  - Day of admission to ICU
  - Biweekly during ICU stay
  - Contact isolation for carriers
  - Transfers from hospitals with high prevalence or from other ICUs
  - Preemptive contact isolation
  - Continuous program of hand hygiene promotion
  - Regular compliance observation
  - Feedback on antibiotic use

Laurent C. ICHE 2008

Effect of contact isolation on prevention of ESBL transmission – example 3

- Routine infection control measures, implemented in October, not sufficient!

Need for reinforced infection control strategies

Laurent C. ICHE 2008
Ruef – Infection control measures

Reinforced infection control strategies

- Daily surveillance cultures for all ICU patients
- Isolation as soon as Vitek 2 result suggested ESBL
- Cohorted care for all ESBL patients
  - Dedicated 6-bed ICU, additional nurses
- Early discharge from ICU
- Postdischarge cleaning and disinfection under supervision of infection control
- Daily meetings between ICU and infection control

Laurent C. ICHE 2008

Effect of contact isolation on prevention of ESBL transmission – example 3

Infection control for ESBL: Conclusions from examples 1-3

- Infection control (contact isolation) not sufficient
- Good infection control (=good compliance) is needed
- Good infection control based on very good compliance probably sufficient
- Antibiotic restriction policy may be an additive measure

Laurent C. ICHE 2008
Ruef – Infection control measures

Role of healthcare worker colonization in ESBL transmission?

- Transient hand colonization documented
  - Chronic hand colonization responsible for transmission of outbreak
    - Association with artificial nails
    - Gupta A. ICHE 2004; 25: 210-215
- GI-tract colonization of HCW very rare
  - Screening of HCW rarely indicated!

Decolonization of patients

- Lack of firm data, some older studies
  - SDD with
    - polymyxin, neomycin, nalidixic acid
    - Colistin and tobramycin
    - Norfloxacin
  - Nasopharyngeal spray with povidone-iodine for respiratory tract colonization during an outbreak in neurological rehabilitation unit
  - No firm recommendation regarding any decolonization strategy!

Ongoing outbreak: consider environmental contamination

- Ultrasound gel
- Bronchoscope
- Glass thermometer
Ruef – Infection control measures

Role of routine surveillance cultures for detection of ESBL colonization

- Estimated proportion of undetected ESBL: 70% (MRSA: 30–90%)
- Surveillance cultures useful during outbreak situation
- Role of surveillance cultures during non-outbreak situation unclear
  - Dependent on local epidemiology
    - Low versus high prevalence of positive clinical samples

Conclusions regarding infection control measures in ESBL – compared with MRSA

<table>
<thead>
<tr>
<th>Measure</th>
<th>MRSA</th>
<th>ESBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact precautions</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Antibiotic restriction</td>
<td>-</td>
<td>+ (additive)</td>
</tr>
<tr>
<td>Decolonization of patients</td>
<td>+ (if feasible)</td>
<td>Unresolved issue</td>
</tr>
<tr>
<td>HCW screening</td>
<td>Outbreak setting</td>
<td>Rarely indicated</td>
</tr>
<tr>
<td>Screening cultures</td>
<td>Local policy</td>
<td>Outbreak, local policy</td>
</tr>
</tbody>
</table>

Infection control interventions appropriate to controlling spread of ESBL-producing organisms within a hospital

- Identify patients infected with ESBL-producing organisms by use of appropriate detection methods in the clinical microbiology laboratory
- Identify colonized patients by use of rectal swabs plated onto selective media
- Perform molecular epidemiologic analysis of strains from infected or colonized patients (for example, by use of pulsed-field gel electrophoresis)
- Institute contact isolation precautions, particularly if clonal spread is demonstrated
- Institute controls on antibiotic use, particularly if numerous strain types are demonstrated

Paterson DL. Clin Microbiol Rev 2005