Antibiotic Therapy and Resistance Patterns in ICU

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Aspects

- Antibiotic resistance
- ESBL
- Genetic basis
- Infection control policies
- Antibiotic control policies
- Antibiotic therapy
- Future directions
Antibiotic resistance

- Past six decades more than 15 classes of systemic antimicrobials have been introduced into clinical practice
- Greatest strides have been made with improvement of hygiene and social conditions!!
- Antibiotic armamentarium is being lost rapidly due to bacterial resistance, which can be disastrous (pre-antibiotic era)
Historical Aspects

• 1941 Albert Alexander first recipient of penicillin
• 1942 first resistant isolates of Staph aureus reported
• 1960 Methicillin introduced
• 1964 first MRSA reported
• 1980s MRSA became major nosocomial infection
Historical aspects

• 1980s – ESBL producing GN bacteria
• 1990 Vancomycin resistant Enterococci emerged
• 2000 VISA (intermediate level resistance)
• 2002-VRSA (high level resistance)
• 2002- Linezolid resistant enterococci and Staphylococci reported
Antibiotic resistance

- Bacterial response to antimicrobial may be rapid or slow onset of resistance
- Once resistance develops in one part of world others should anticipate it.
- Antibiotic resistance is greatest in ICU large teaching hosp and medical centers and spreads to general wards and smaller hosp
ICU: the" hotspots"

• Greater severity of illness
• Increased use of invasive devices
• Colonization /infection by multiresistant bacteria
• Empirical use of antibiotics
• Relative overcrowding
• Health care staff busy
• Promotes spread from patient to patient
Antibiotic resistance

• Resistant strains are as virulent as their susceptible relatives and cause higher morbidity/mortality.
• For every new drug introduced there are resistance mechanisms in the bacteria waiting to emerge

“Depressing evolutionary progress”
Resistance equation

• Risk of emergence antibiotic resistance

- Antibiotic pressure
- Genetic selection
- Risk of cross infection
Genetic basis

Genetic selection underlies all resistance
Some single amino acid substitution by mutation (ESBL) are rapid and some need multiple genes to cause resistance (VRE)

- Mutations
- Plasmids
- Transposons
- Integrons
Beta Lactamases

• Major defence of GNB against B lactams
• Hundreds have co-evolved with newer drugs
• Spread from Staphylococci to H Influenzae and N gonorrhoeae
• With over-use of new B lactams in last 2 decades “new” Extended spectrum beta lactamases(ESBLs), carbapenemases
Beta Lactamases

• Classified based on Prim structure
  – Class A (Serine residue)
  – Class B (metallo-enzyme)
  – Class C (Serine residue)
  – Class D (Serine residue)

• Class A&D - plasmid mediated
• Class B&C - encoded by chromosomal genes
New Beta lactamases

- TEM type ESBL
- SHV type ESBL
- CTX type ESBL
- OXA type ESBL
- Plasmid mediated Amp C enzymes
- Carbapenemases
ESBL

- TEM type - 130 types
- 10, 12 and 26 commonest
- Active against oxyamino B lactams (3rd gen CS) and aztreonam
- Usually susceptible to B lactamase inhibitor
ESBL

- **SHV type** - 50 types
- Similar structure and activity
- 5,12 most common
- Predominant in Europe and America
ESBL

• **CTX-M type**: greater activity against Cefotaxime
• Same activity as TEM/SHV
• Some hydrolyze Ceftazidime and cefepime faster
• 40 types known
• Type 3,4,14 common
ESBL

- **OXA type**: greater activity against Oxacillin
- Spectrum same as CTX
- Mainly found in Pseudomonas
- Resistant to Clavulanic acid
Diagnosing ESBL

- Most microbiologic labs do not routinely screen for ESBL production
- No universal marker for ESBL- ceftazidime resistance “surrogate” marker
- Enterobacteriaceae having ceftazidime MIC ≥2 ug/ml are likely ESBL
- Inoculum effect - AB sensitive in vitro may fail in vivo due to increase in MIC with bacterial load

- George KH et al AJRCCM , 2000
Diagnosing ESBL

• NCCLS has recommended screening for ESBL *K pneumoniae* and *E coli* with reduced susceptibility to cefotaxime, ceftriaxone, ceftazidime and Aztreonam

• Confirmation by various tests:
  – Double disk approximation,
  – Three dimensional agar test
  – ESBL card (Vitek)
  – ESBL strip (Etest) [Investigational]

- Patterson JE, SRCCM 2003
Amp C Enzymes

- Inducible by β-Lactam drugs
- Encoded by chromosomal genes in GNB
- Enterobacter Cloacae, Klebsiella, E coli and Salmonellae may easily transfer the resistant genes by plasmids
- 20 types known
- Spectrum 3rd gen CS + cephamycins
- Resistant to clavulanic acid
Carbapenemases

- Currently uncommon
- Enterobact, Acinetobac and Pseudomonon
- IMP type plasmid mediated first in Japan (90) have spread to Europe(97), Far east
- VIM family reported from Italy (99) have spread to USA and far east
- Spectrum - ES + carbapenems
Transposons

- Mobile unit of DNA that can jump from one molecule to another usually without site specificity
- From plasmid/chromosome of a bacterium to another plasmid/chromosome thus transferring resistance genes with it.
Integrons

“Adding another threat to antibiotic use”

• Integrons are mobile genetic elements which capture and spread genes by site specific recombination
• Integron bearing Enterobacteriaceae can lead to inter and intraspecies transfer of resistance
• Cross transmission in ICU by health care personnel can lead to alarming rise of resistance

Norby RS Clin Infect Dis Jul 05
Linezolid resistance

• Approved for VREF, MRSA Apr 2000
• Emergence of resistant enterococci and MRSA (rare- 08 / 9833 isolates ~ 0.08% )
• Used with caution in
  – Poor penetration sites /infected FB
  – Lengthy /repeated courses (CAPD peritonitis)
  – Long term oral treatment (CF)
  – Undergoing hemodialysis

Venkata GM Clin Inf dis 2004
Combating Resistance

2 major factors

- Poor infection control
- Selective antibiotic pressure

Rice LB Cleveland Clin J Med Oct 2003
Combating Resistance

• Active surveillance for resistance
• Enforce infection control policies
• Special Nursing Care
• Restrict use of antibiotics
• Antibiotic rotation/cycling
• Selective Decontamination of digestive tract (SDD)

Kollef MH, Ann Intern Med 2001
Active surveillance

• Provide understanding of local bacterial flora and resistance patterns
• Cultures must be obtained from suspected sites before empirical antibiotics
• Routine surveillance cultures from respiratory and perianal region for “isolation” of colonized patients

Weinstein RA, Sem in Resp & Crit care Med 2003
Molecular typing

• High resistance rates: investigated by pulse field gel electrophoresis
• Single strain – person to person spread or common source due to lax hygiene
• Multiple strains- emergence of drug resistance due to antibiotic pressure or exogenous introduction of bacteria
• Both may frequently coexist

Weinstein RA, Sem in Resp & Crit care Med 2003
Hand Hygiene

• Should be stressed at all times
• Rates are low due to increased workload, perceived damage by frequent use of soap
• Requires 90 mins per shift if done as recommended by CDC
• **Solution**!!! Alcohol based hand rubs are useful as they reduce time spent (3-4 fold) and are bactericidal

Special Nursing Care

- Education and monitoring: best compliance level hand washing achieved ~ 60-80%
- When colonization pressure are high (>50%) even this level cannot prevent transmission
- Contact isolation: universal gloving for all contact with colonized patients followed by disinfection with alcohol rubs
- Cohort Nursing: patients colonized VRE are cared by separate nurses
- Requires adequate staffing of the ICU

*Weinstein RA, Sem in Resp & Crit care Med 2003*
Hands & VRE

• VRE transmission in ICU by carriage on hands of care givers
• Enterococci persist for 60 min on unwashed hands
• Patients skin colonized more freq if diarrhea or incontinence (esp. Cl Difficille)
• Indirect contact with bedrails or table tops (cocci can survive for ~7 days)
• VRE can be carried on uniforms and equipment stethoscopes

_Weber SG, Sem in Resp & Crit care Med 2003_
Infection control

• 29% of clinicians hands became contaminated with VRE despite use of hand gloves
• Use of gowns & gloves vs gloves alone reduced VRE acquisition from 19.6 to 9.1 per 1000 patient days in a Med ICU
• Use of gloves and cover gown in caring infected or colonized is recommended

Antibiotic pressure
Antibiotic policy

• Restricting the use of antibiotics: minimize the unnecessary use in hospitals

• Antibiotic administration – proper dose, intervals and optimal duration (↓ bacterial resistance and drug side-effects)

• Follow local guidelines drawn by Clinicians and microbiologists based on clinical and surveillance data for ICU

*Kollef MH, Ann Intern Med 2001*
“Narrow” spectrum antibiotics

• For community acq pneumonia, UTI which are not life threatening narrow spectrum agents (penicillin, gentamicin, TMP) be used instead of broad spectrum cephalosporins

• Using this strategy with infection control policies reduced Cl difficile infections

- Kollef MH, Ann Intern Med 2001
Older ABs

- Bacteremia isolates for 14 years (1981-95)
- 8840 isolates from 7938 episodes
- Enterobacteriacea resistant to 3G Cs, carbpen, AG and FQ was found to be very low < 1% !!
- Routine treatment for bacteremia used: Pen G / ampicillin + AG
- Successful use of old narrow sp AB to minimize resistance in bacteria

Kollef MH Ann Intern Med 2001
Antibiotic prescription

• Restriction of use by clinicians
  – Antibiotic order forms
  – Concurrent feedback

• Hospital Formulary based restriction
  – Certain drugs are restricted in situations
  – ESBL(3 Gen CS) VRE (Vancomycin)

• Computer based antibiotic restriction
  – Reduced cost, AB use and resistance rates
  – Without adverse effects on clinical outcome

Hospital infection control committee audits the data and issues guidelines for empiric therapy

Weinstein RA, Sem in Resp & Crit care Med 2003
Antimicrobial Strategies

Limit unnecessary antibiotic administration
• Develop hospital-based guidelines for antibiotic use
• Create an antibiotic use quality improvement team
• Provide education and professional detailing on antibiotic use for physicians
• Create a national intervention policy restricting antimicrobial use
• Develop guidelines with a multidisciplinary approach, involving local and national peer leaders
• Restrict the hospital formulary
• Use narrow-spectrum or older antibiotics
• Use quantitative cultures and quantitative assessments for nosocomial pneumonia

Optimize antimicrobial effectiveness
• Avoid inadequate treatment by using automated guidelines
• Use combination antimicrobial treatment
• Use antibiotic cycling and scheduled antibiotic changes
• Use area-specific empirical antimicrobial therapy
• Limit short-course antibiotic prophylaxis to clinically validated indications
• Avoid routine antimicrobial decontamination of the aerodigestive tract

Kollef MH, Ann Intern Med 2001
## Restricted Antibiotic use

<table>
<thead>
<tr>
<th>study</th>
<th>country</th>
<th>pathogen</th>
<th>intervention</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahal et al.</td>
<td>United States</td>
<td>ESBL-producing <em>Klebsiella</em> species</td>
<td>Hospital-wide restriction of cephalosporin</td>
<td>Reduction of infection due to ESBL-producing <em>Klebsiella</em> species</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased infection due to imipenem-resistant <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Climo et al. (77)</td>
<td>United States</td>
<td>Clindamycin-resistant <em>Clostridium difficile</em></td>
<td>Restricted use of clindamycin</td>
<td>Overall reduction in clindamycin use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduction in cases of <em>C. difficile</em>–associated diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased susceptibility of <em>C. difficile</em> to clindamycin</td>
</tr>
</tbody>
</table>
| Quale et al. (States) | 78, 85 United | Vancomycin-resistant enterococci              | Restricted use of vancomycin  
Restricted use of cephalosporins  
Addition of β-lactamase inhibitors to formulary | Decreased point prevalence of fecal colonization with vancomycin-resistant enterococci                                                |

*Kollef MH, Ann Intern Med 2001*
Antibiotic rotation policy

• AB class cycling or rotation has potential for reducing resistance (Withdrawn for a defined period and reintroduced later)
• Bacterial isolates regain sensitivity
• Reduction in infective episodes and mortality
• Reduction in prevalence of MRSA, VRE and ESBL producing GNB
• Useful strategy to combat the antibiotic crisis due to rapid development of resistance

Pechere JS, Critical Care Med Feb 2002
Antibiotic rotation

- Optimal duration of cycles not established
- Class of drugs are used for empiric therapy for said period (3-4 mths)
  - 3 gen Cephalosporins
  - Flouroquinolones
  - Piperacillin –tazobactam
  - carbapemnems
## Antibiotic cycling

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<th>intervention</th>
<th>outcome</th>
</tr>
</thead>
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<tr>
<td>Kollel et al.</td>
<td>United States</td>
<td>Increasing resistance of gram negative bacteria to ceftazidime</td>
<td>Scheduled ICU-wide change to ciprofloxacin for empirical gram-negative treatment</td>
<td>Reduced occurrence of ventilator associated pneumonia and bloodstream infections reductions in ceftazidime-resistant gram-negative bacterial infection</td>
</tr>
<tr>
<td>Kollel et al.</td>
<td>United States</td>
<td>Increasing resistance of gram negative bacteria to ceftazidime</td>
<td>Scheduled ICU-wide changes to ciprofloxacin(6 months) followed by cefepime (6 months) for empirical treatment</td>
<td>Reduced administration of inadequate empirical antimicrobial treatment during the two antibiotic change</td>
</tr>
<tr>
<td>Gruson et al.</td>
<td>France</td>
<td>Increasing resistance of gram negative bacteria to ceftazidime and ciprofloxacin</td>
<td>Restricted use of ceftazidime and ciprofloxacin</td>
<td>Reduced occurrence of ventilator associated Pneumonia Reduced administration of inadequate empirical antimicrobial treatment</td>
</tr>
</tbody>
</table>

*Kollef MH, Ann Intern Med 2001*
Selective Decontamination

Selective decontamination of digestive tract employs four components
- Topical antibiotics
- Systemic antibiotics
- Infection control policies
- Surveillance cultures to monitor progress

Aim to selectively eliminate aerobic Gram-negative bacilli and yeast from the mouth and stomach to reduce the occurrence of nosocomial infections
- Controversial as some studies have shown emergence of resistant strains (MRSA, VRE)

Kollef MH, Chest 2003
## Agents used: SDD

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Target</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>Aerobic gram negative bacteria</td>
<td>topical</td>
</tr>
<tr>
<td>Polymixin B</td>
<td>Aerobic gram negative bacteria</td>
<td>topical</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Candida /other yeasts</td>
<td>topical</td>
</tr>
<tr>
<td>Cefotaxime/ceftriazone</td>
<td>Aerobic gram negative &amp;positive bacteria</td>
<td>systemic</td>
</tr>
</tbody>
</table>

*Kollef MH, Chest 2003*
SDD: meta-analysis

- Two meta-analysis of 53 RCT involving 8500 patients
- Has been effective in reducing Lower airway infection OR 0.35(0.29-0.41) and mortality OR 0.80(0.69-0.93)
- 6% overall mortality reduction from 30 to 24%
- No demonstrable increase in infection due to resistant bacteria

_Hendrick KF Intens Care Med 2003_
Controversies: SDD

- Effects of SDD are due to enteral or parenteral drugs
- SDD has shown benefit in series with surgical and trauma patients (known to benefit from system antibiotic prophylaxis)
- Lack of standard definition of SDD
- Variable practice of SDD in various centers
SDD & resistance

- Alters normal intestinal flora and promotes bacterial overgrowth and colonization with resistant pathogens
- Increase in pneumonia due to Staph, Acinetobacter and bacteriemia due to staphylococci & Enterococci
- Antibiotic resistant strains emerge (AG & FQ resist GNB, MRSA)

Kollef MH, Chest 2003
SDD utilization

• Fears of antibiotic resistant strains: SDD has not gained popularity
• European Consensus conference, 279 ICU physicians were interviewed
  – 18% use for all on MV
  – 50% never use
  – 32% selective use (outbreak of MDR, specific diagnosis)

Misset B et al Inten Care Med 1996
SDD recommendations

Based on the available evidence and experience with SDD and the likelihood of emergence of resistant bacteria, the routine or indiscriminate clinical use of SDD cannot be recommended at the present time.

Kollef MH, Chest 2003
Summary of strategies

Antibiotic therapy
Surveillance Programmes

• Networks that monitor bacterial isolates and resistance patterns from centers worldwide - comprehensive data for guiding empiric therapy

• NNIS (CDC)
• MYSTIC
• SENTRY
• ICARE
Pneumonia : SENTRY (97-01)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S. aureus</td>
<td>22.9–25.6%</td>
</tr>
<tr>
<td>2</td>
<td>P. aeruginosa</td>
<td>18.1–18.7%</td>
</tr>
<tr>
<td>3</td>
<td>H. influenzae</td>
<td>9.4–10.3%</td>
</tr>
<tr>
<td>4</td>
<td>S. pneumoniae</td>
<td>7.7–7.8%</td>
</tr>
<tr>
<td>5</td>
<td>Klebsiella sp.</td>
<td>7.0–8.7%</td>
</tr>
<tr>
<td>6</td>
<td>Enterobacter sp.</td>
<td>6.7–7.4%</td>
</tr>
<tr>
<td>7</td>
<td>E. coli</td>
<td>4.3–4.7%</td>
</tr>
<tr>
<td>8</td>
<td>S. maltophilia</td>
<td>3.6–4.1%</td>
</tr>
<tr>
<td>9</td>
<td>S. marcescens</td>
<td>2.6–3.4%</td>
</tr>
<tr>
<td>10</td>
<td>Acinetobacter sp.</td>
<td>2.3–3.0%</td>
</tr>
</tbody>
</table>

Rank order of pathogens respiratory specimen from 5530 isolates

Seminars in Resp and Crit Care Medicine, 2003
**BSI: SENTRY 1997-2001**

<table>
<thead>
<tr>
<th></th>
<th>Pathogen</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>S. aureus</em></td>
<td>22.9–28.7%</td>
</tr>
<tr>
<td>2</td>
<td><em>E. coli</em></td>
<td>16.7–18.6%</td>
</tr>
<tr>
<td>3</td>
<td>Coag neg Staph</td>
<td>10.6–12.8%</td>
</tr>
<tr>
<td>4</td>
<td><em>Enterococcus sp</em></td>
<td>9.5–10.6%</td>
</tr>
<tr>
<td>5</td>
<td><em>Klebsiellas sp</em></td>
<td>7.4–7.8%</td>
</tr>
<tr>
<td>6</td>
<td>Viridans streptococci</td>
<td>4.6–5.6%</td>
</tr>
<tr>
<td>7</td>
<td><em>S. pneumoniae</em></td>
<td>3.4–5.6%</td>
</tr>
<tr>
<td>8</td>
<td><em>P. aeruginosa</em></td>
<td>3.9–4.6%</td>
</tr>
<tr>
<td>9</td>
<td><em>Enterobacter sp</em></td>
<td>3.3–4.1%</td>
</tr>
<tr>
<td>10</td>
<td><em>P. mirabilis</em></td>
<td>1.5–1.6%</td>
</tr>
</tbody>
</table>

Rates of Blood stream infection pathogens from 35,386 episodes

Seminars in Resp and Crit Care Medicine, 2003.
Profile of VAP (AIIMS)

- Retrospective study, Apr03 - Mar 04
- Non bronchoscopic BAL, quantitative culture
- Organism >10^4 cfu/ml was indicator of VAP
- 171 of 478 samples signif growth (35.77%)
- 192 isolates =190 GNB, 2MRSA
- Acinetobacter 44.8%, pseudomonas 40.1%, Klebsiella 5.7% ,E coli 4.2% ,others 3.6%
- ESBL producing GNB were 181(95.3%)!!
- Polymicrobial VAP 12.3%

Singhal R, Ind J med Res Jan 05
VAP profile: PGIMER

Culture positivity rate 51.9% (5.2% polymicrobial)
Most commonly tracheobronchial secretion

- Acinetobacter spp. 34.8%
- Ps. Aeruginosa 23.9%
- E. coli 15.2%
- Meth. res. Staph. aureus 8.7%
- Alkalegenes fecalis 4.3%
- Klebsiella pneumoniae 2.2%
- Candida spp. 4.3%
- Miscellaneous 6.5%

Agarwal R et al 2003 (unpublished data)
HAP

• Early onset HAP: within 4 days after hosp caused by sensitive pathogens
• Late onset HAP: After 5 days of hosp caused by MDR pathogens, carries high morbidity and mortality
• Early onset HAP with risk factors are also likely to due to MDR pathogens

ATS guidelines AJRCCM, 2005
Risk factors for HAP/HCAP

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

ATS guidelines AJRCCM, 2005
Increased mortality: VAP

VAP associated with attributable mortality of 33-50% which increases further

- Acinetobacter, Pseudomonas infection
- Bacteremia
- Medical illness > surgical illness
- Inappropriate antibiotic therapy
- Delayed Antibiotic therapy

- ATS guidelines AJRCCM, 2005
“Appropriate” therapy

- Mortality was higher if inappropriate therapy was used (52.1% vs 23.5%, p<0.001)
- multiple logistic regression for confounding variables supported hypothesis
  
  Adjusted OR 4.26

Kollef MH, Chest 1999
Early therapy

- VAP 3Trt gps: at first suspicion, after FOB, BAL & after BAL results obtained.
- Mortality was significantly higher compared to prompt therapy.
- Data from FOB may be available too late to affect survival.

Luna CM et al. Chest 1997
Empiric Therapy

- **Diagnosis of VAP**: difficult in critically ill patients
- **Mimickers**: atelectasis, pulmonary hemorrhage, drug reaction, pulmonary edema, ARDS, PTE

- **sTREM-1** soluble triggering receptors expressed on myeloid cells in BAL by rapid immunoblot technique - strong independent predictors of pneumonia (148 patients, suspected VAP OR 41.5)

*ATS guidelines, AJRCCM 2005*
Tracheobronchitis

Nosocomial tracheo-bronchitis: purulent secretions, signs of infection with normal radiograph and culture positive

- associated with longer ICU stay and MV, without increased mortality.
- Antibiotic therapy may be beneficial to this group of patients

- ATS guidelines, AJRCCM 2005
Crude mortality VAP vs Purulent Tracheobronchitis

Acinetobacter and Pseudomonas

Fagon et al., Am Rev Respir Dis 1989;139:877–884
Empiric Therapy

• Most accurate criteria for starting ABs
  – New or progressive radiological infiltrates
  – 2 of 3 clinical features: fever >38C, leucocytosis or leucopenia, purulent tracheal secretions

• Microbiological cultures of lower resp tract secretions should be used to confirm the diagnosis and guide further therapy after 48-72h.

ATS guidelines, AJRCCM 2005
“Appropriate” therapy

- Time of onset of VAP and risk factors for drug resistant pathogens
- Local microbiological flora and resistance pattern of the ICU
- Tracheal aspirate for gram stain used to guide initial therapy can reduce inappropriate therapy
- Broad spectrum combinations may also reduce inappropriate initial therapy to < 10%

ATS guidelines, AJRCCM 2005
Early VAP/HAP

- Streptococcus pneumoniae
- Haemophilus influenzae
- Methicillin sensitive Staphylococcus aureus
- AB sensitive GNB
- Ceftriaxone or
- Levoflox/moxifloxacin or
- Amplicillin-sulbactam or
- Ertapenem

ATS guidelines, AJRCCM 2005
Late VAP/HAP

- Pseudomonas aeruginosa
- Acinetobacter sp
- Klebsiella pneumoniae
- E coli
- Methicillin resistant Staph aureus (MRSA)
- Cefepime/ceftazidime
- Piperacillin-tazobactam
- Imipenem/meropenem
- Quinolone
- Aminoglycoside
- Vancomycin or linezolid

ATS guidelines, AJRCCM 2005
Duration: 8 vs 15 days

- Prospective RDBCT of VAP, French ICU
- 401 VAP = 197 X 8 days, 204 X 15 days AB
- Neither excess mortality nor relapses in 8 days group and sign more mean AB free days (8.7 vs 13.1d p < 0.001)
- ICU stay, MV days, organ failure days: same
- Pseudomonas VAP higher recurrence rate 40.6 vs 25.4% with 8 days therapy (mortality similar)
- Recurrent VAP MDR pathogen were less in 8 days as compared to 15 days 42.1 vs 62% , p=0.04)

Duration of therapy

- Prospective, RCT, MICU
- 290 Clinically suspected VAP
- Duration of AB was determined by antibiotic discontinuation policy or their treating physician
- AB duration was significantly shorter (6+4.9 vs 8+5.6 days, p=0.001) in discontinuation arm
- No difference in mortality, recurrence of VAP or ICU stay between two groups
- Shorter courses of empiric therapy can be safely achieved

Micek TS et al, Chest 2004
Duration of therapy

• Duration of 7-8 days is recommended for uncomplicated VAP with good clinical response to treatment

• For Non lactose fermenting organisms (Pseudomonas and Acinetobacter) longer duration to prevent relapses

- ATS guidelines, AJRCCM 2005
Monotherapy

- Early HAP with no risk factors for MDR pathogens
- Documented gram +HAP (MRSA)
- Mild HAP (CPIS <6)
- Agents: Quinolones/ carbapenemems/ piperacillin- tazobactam

ATS guidelines, AJRCCM 2005
Combination therapy

• Meta-analysis: 7586 patients with sepsis (~1200 were HAP / VAP)
  – clinical failure more with combination therapy
  – no advantage in Pseudomonas infections
  – did not prevent antibiotic resistance strains
  – more nephrotoxicity

Paul M et al BMJ Mar 2004
Monotherapy Vs combination

- Pseudomonas infection – synergistic effect documented in neutropenic host and bacteremia
- Prevent emergence of antibiotic resistance with Pseudomonas & Enterobacter strains.
- Initial empiric therapy for late onset HAP/ with risk factors for MDR pathogens as inadequate therapy assoc with mortality.

ATS guidelines, AJRCCM 2005
“Clinicians working in ICUs are faced with the paradox of having to prescribe broader initial empiric antibiotic treatment to patients suspected of having VAP while trying to minimize further emergence of antibiotic resistance”

-Kollef MH, Chest 1999
Antibiotic therapy

• Early and appropriate therapy—based on local data of bacterial infections & resistance patterns “Get it right the first time”
• Avoid changing before 48-72 hours: time required for clinical response unless rapid deterioration occurs
• Prompt de-escalation of therapy
• Avoid unnecessary AB: unless strong clinical or microbiological evidence of infection “colonisation should never be treated”
Treatment Algorithm

ATS guidelines, AJRCCM 2005
# Big five bugs

<table>
<thead>
<tr>
<th>Organism</th>
<th>First line Drugs</th>
<th>Second line Drugs</th>
<th>Infection control</th>
</tr>
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<tr>
<td>Ps aerug</td>
<td>Cefep/Piptazo+ quinolone/AG</td>
<td>carbapenm+ quinolone/AG</td>
<td>+</td>
</tr>
<tr>
<td>Acinetob</td>
<td>Carbapenem</td>
<td>ampi+sulbact / Colistin</td>
<td>+</td>
</tr>
<tr>
<td>Kleb pne</td>
<td>carbapenem</td>
<td>Piptazo</td>
<td>3 gen CS(CZ)</td>
</tr>
<tr>
<td>ESBL+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin</td>
<td>Linezolid</td>
<td>+</td>
</tr>
<tr>
<td>VRE</td>
<td>linezolid</td>
<td>streptogramin</td>
<td>+++</td>
</tr>
</tbody>
</table>
Future antibiotics

- Beta lactams - Cephem, C2 modified and methyl carbapenem
- Glycopeptides – Oritavancin, Dalbavancin, telavancin
- Cyclic lipopeptodes- Daptomycin
- Oxazolidinones- Eprezolid, ranbezolid
- Tetracyclines- Tigecycline
- Lipoglycodepsipeptides - Ramoplanin

- Blasi Fet al  Curr Opin Pulm Med 2004
Novel therapies

**Cationic peptides:** naturally produced render bacteria more susceptible to immune mechanisms and antimicrobials

- Defensins
- Granulysin
- Protregrin (Iseganan aerosol phII Clin trial in CF)

**Peptide deformylase inhibitors** enzyme essential for bacterial growth (BB83698 promising)

- *Blasi Fet al Curr Opin Pulm Med 2004*
Future directions

- Monoclonal Antibody (tefibazumab-MRSA)
- Blocking bacterial adhesion – peptides against fimbria of pseudomonas
- Inactivation of genes responsible for cell wall modification in MRSA
- Future may find scientists inactivating of genes which led to bacterial resistance

- Deresinski S, Clin Infec Dis 2005
let us all join hands to fight this menace

Thank you