ANTIBIOTIC EFFICACY AND SAFETY

What should the clinician know in 2001?

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Current Antibiotic Problems

- Resistance
- Infrequent use of diagnostic tests
- Inappropriate efficacy documentation
- Irrelevant safety documentation
- Safety problems
- No new antibiotics against multiply resistant Gram-negative pathogens

What Is Resistance?

- Reduced susceptibility leading to treatment failures? **YES,** if you are a clinician or a patient.
- Something decided by NCCLS, BSAC and similar organisations? **YES**, if you are a clinical microbiologist.
- Presence of a resistance gene? **YES**, if you are an epidemiologist.

Interpretation Problems

- A strain of *E. coli* inhibited by 2 mg/L of cefotaxime is classified as sensitive by most systems despite the fact that it is appr. 2000 times less susceptible than a normal strain.
- A strain of *S. pneumoniae* with a penicillin MIC of 2 mg/L is called resistant despite plasma concentrations >100 mg/L

Resistance Surveys

- Tend to overemphasise problems (samples are taken when something is wrong)
- Often include duplicate isolates
- Rarely prospective and virtually never denominator driven

Resistance is a global problem which must be monitored locally. Surveys may be biased.

Resistance Problems (1)

(N=nosocomial; C=community)

1. Gram-positive organisms

- **Staphylococci** - methicillin, glycopeptides **N (C!)**
- **Pneumococci** - beta-lactams, co-trimoxazole, macrolides **C**
- **Enterococci** - beta-lactams, glycopeptides **N**

Resistance Problems (2)

2. Gram-negative organisms

- Enterobacter, serratia, pseudomonas a.o. - Type I cephalosporinase **N**
- E. coli, klebsiella, enterobacter – ESBLs **N**
- Pseudomonas, acinetobacter stenotrophomonas - carbapenems a.o.**N**

Resistance Problems (3)

3. **Mycobacteria**

- *Mycobacterium tuberculosis* **N C**
- Atypical mycobacteria, especially *mycobacterium avium intracellulare* **C**

Resistance Problems (4)

4. Antifungals

- Extensive use of azoles, e.g. for prophylaxis, has resulted in a marked increase of infections caused by azole-resistant *Candida* spp. other than *C. albicans*, mainly *C. glabrata* and *C. krusei*

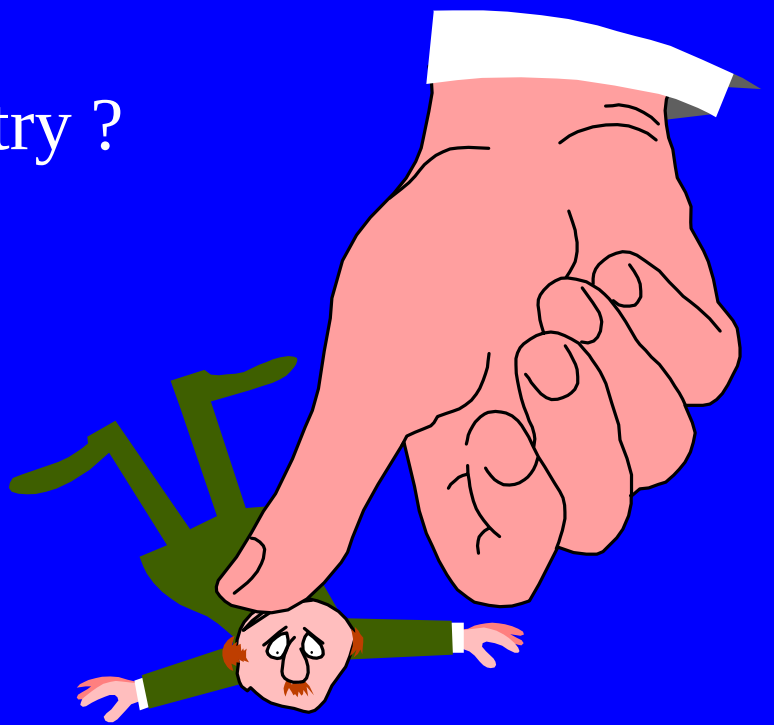
Resistance Problems (5)

5. Antivirals

- Acyclovir-resistant Herpes simplex can be seen but not a major problem
- Resistance in HIV major problem

Who To Blame ?

- The veterinarians ?
- The pharmaceutical industry ?
- The pharmacists ?
- The physicians ?
- The patients ?



Veterinary Use: Issues (1)

- Do antibiotics in animal feed and/or therapy/prophylaxis of animal infections (i) lead to emergence of resistance and (ii) if that is the case, can such resistance be transferred to man?
- Are all antibiotics alike or are there culprits more likely to cause resistance problems?

Veterinary Use: Issues (2)

- Enrofloxacin, a veterinary FQ with a spectrum similar to ciprofloxacin´s was introduced in continental Europe 1987 and in the UK 1993. Emergence of FQ-resistant *Campylobacter* spp. and multi-resistant *Salmonella typhimurium* in poultry and meat may be a consequence of extensive use of enrofloxacin.

FQ-resistant campylobacter (1)

- In 1993/94 UK bred chickens and chicken from continental Europe were compared. 37/64 (58%) UK chickens contained campylobacter and 1 strain (2.7%) was ciprofloxacin-resistant. Of non-UK chickens 26/50 (52%) contained campylobacter and 7 strains (27%) were resistant (Piddock JAC 1995;36:891).

FQ-resistant campylobacter (2)

- FQ-treated, campylobacter-infected chickens all had FQ-resistant strains after treatment and 181/617 (29%) isolates were FQ-resistant prior to treatment and persisted (Jacobs-Reitsma et al. Letters Appl Microbiol 1994;19:228).

Salmonella typhimurium DT104 (1)

- Multiresistant (including FQ) isolates of *S. typhimurium* phage type DT104 isolated from poultry or meat have increased in frequency in the UK since 1993, i.e., since the approval of enrofloxacin (Threlfall et al. Microb Drug Res 1997; 3: 263)

Salmonella typhimurium DT104 (2)

- In the UK 9/23 (39%) cases of human infections with *S. typhimurium* DT104 occurred in farmers or their families (Fone & Barker Commun Dis Rep Cdr Rev 1994; 4: r136)

Ciprofloxacin-Resistant Salmonella

(Threlfall et al. Microb Drug Res 1997;3:263)

Salmonella species	Frequency of resistance	
	1994	1996
S. enteritidis	<1%	<1%
S. typhimurium	1%	12%
S. virchow	5%	11%
S. hadar	40%	60%

FQ resistance in Spain (1)

Cruchaga et al. JAC 2001;47:315

Salmonella species and source		% resistance Cip	Nx
S enteritidis	human (N=385)	0	31
	food (N=125)	0	23
	animal (N=13)	0	15

Cip=ciprofloxacin; Nx=nalidixic acid

FQ resistance in Spain (2)

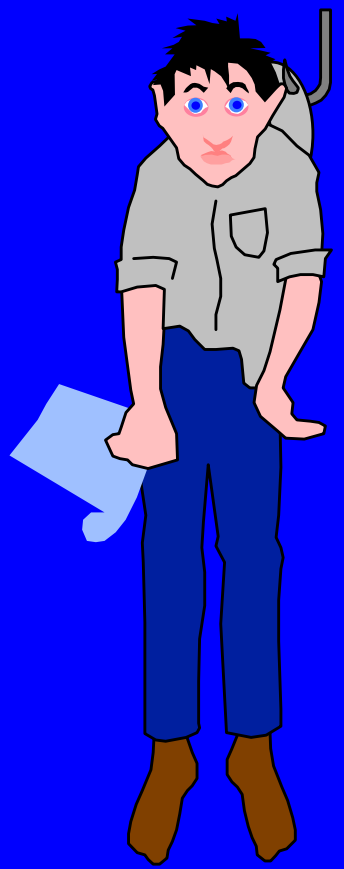
Salmonella species and source	% resistance	
	Cip	Nx
S. typhimur. human (N=284)	1	6
food (N=67)	0	3
animal (N=127)	8	76

FQ resistance in Spain (3)

Salmonella species and source		% resistance Cip	Nx
All	human (N=1051)	0.6	26
	food (N=420)	0.6	27
	animal (N=238)	5	48

Veterinary uses : conclusions

- Veterinary use leads to resistance in bacteria causing infections in man
- Use of antibiotics as growth promotors and for mass prophylaxis should be banned



Pharmaceutical Industry and Resistance

- Resistance is an incentive to develop new drugs
- The cost for development of a new antibiotic is appr. US$600,000,000, to be reclaimed in 3 years. This can be achieved by moderate use and very high price or very high usage and a moderate price.
- Industry thrives from abuse!

Industry Overemphasises the Resistance Problem

- Most large surveillances industry sponsored
- In trials of new quinolones and of other antibiotics for use in adult community acquired pneumonia <1% of the infections were verified to be caused by pneumococci resistant (MIC >1 mg/L) to penicillin. Still the risk of resistant pneumococi in pneumonia is the main marketing argument

The Pharmacists and Resistance

- In many countries (also in Europe) antibiotics are available OTC
- Preferably, availability on prescription only should be enforced by the authorities
- If official sanctions are not possible, pharmacists should be educated

Role of the Physicians

- In most countries the physicians must be blamed for emergence of resistance
- Systems which allow doctors to distribute drugs at a profit seems to promote overuse of antibiotics
- Obvious need for educational efforts

Role of the Patient

Antibiotic use in 2 Swedish communities

- A – high mean family income: 6 antibiotic treatments/year/child in children aged 1-3 with dominance of broad spectrum antibiotics
- B – low mean family income: 3 antibiotic treatments/year/child with dominance of penicillin V

Other factors ...

Factors Related to Antibiotic Consumption

- No. of physicians
- Distance to physician
- No. of physicians in private practice
- Patient´s family income and education

Cost of Resistance

- Increased risk for failures and/or deaths
- Cost for treatment of a normal TB case is appr. $400 – cost for treatment of a MDR TB case is estimated at $80,000
- Resistance often results in increased use of new and very expensive drugs

Is there light at the horizon ?

Linezolid

- Oxazolidinone
- The first truly new antibiotic in 30 years
- Protein synthesis inhibitor at ribosomal level
- Highly active against Gram+ves; *S. aureus (incl. MRSA, MRSE), S. pneumoniae* (incl. PRP), *Enterococcus* spp. (incl. VRE), etc.

Is there light at the horizon ?

- Available for both oral and i.v. Use
- High degre of safety **but** prolonged treatment (<14 days) seems to give some risk for haematological adverse events.
- Expensive

Is there light at the horizon ?

Telithromycin

- Ketolide, i.e., a macrolide type of antibiotic
- High degree of Gram+ activity including PRP, MRSA and MRSE and erythromycin-resistant pneumococci
- Boarderline activity against enterococci and little activity against *H. influenzae*

Is there light at the horizon ?

- Oral only
- Favourable safety profile

Is there light at the horizon ?

New quinolones

- Clinifloxacin, gatifloxacin, gemifloxacin, moxifloxacin, 6-desfluoro quinolones, etc.
- General charactersitics are improved activity against Gram+ organisms but no improvement of the Gram- activity compared to ciprofloxacin

Is there light at the horizon ?

- Oral and (for some) i.v. use
- Safety problems to consider for all quinolones: QTs prolongation, phototoxicity, liver toxicity, tendon ruptures and multi-organ failure
- Paediatric development ongoing; may increase the risk of emergence of resistant pneumococci

Diagnostic tests

+	-
• Reduce antibiotic use if results are followed • Educational • Rapid (some, e.g. GABHS antigen, nitrate stick, CRP, Mono-Spot)	• Cost • Time

Inappropriate Efficacy Documentation

Dilution

- In trials of antibiotics in respiratory tract infections, aetiology is normally verified in <50% of patients. It can be assumed that a large proportion have viral infections
- The probablity of detecting a difference between 2 regimens declines and the true type II error increases

Inappropriate Efficacy Documentation

Lack of representativity

- Ceftriaxone was licensed for use in *Haemophilus influenzae* meningitis based on results in appr. 400 patients, 1 (0.25%) of whom died. Normal fatality rate is at least 5%.

Inappropriate Efficacy Documentation

- No industry sponsored trial of antibiotic use in nosocomial pneumonia in ICU patients has showed higher mortality than 5% - normal mortality is >25%

Inappropriate Efficacy Documentation

What needs to be done?

- In addition to large intention-to-treat (ITT) trials, we need trials in smaller groups of patients with well verified aetiology
- Eliminate as many exclusion criteria as possible in ITT trials
- Increase the influence of independent experts

Safety Documentation Incidents

- Cephaloridine nephrotoxicity
- Moxalactam bleeding
- Temafloxacin multiorgan failure
- Grepafloxacin cardiotoxicity
- Sparfloxacin phototoxicity
- Trovafloxacin liver toxicity

All had been extensively used before the problems became obvious

Safety Documentation Incidents

- In 1991 Norrby & Pernet published an article emphasising that the safety documentation of temafloxacin was the so far most extensive and detailed.
- Two weeks later temafloxacin was withdrawn due to multiorgan failure in 1/4000 treated patients

Safety Registration Problems

Dilution and bias

- Registration of **events** gives adverse events in 30-40% of placebo treated patients
- Investigators are required to state probablity of correlation between observed event and drug given – invites bias

Safety Registration: solutions ?

Suggestions

- Whenever possible, use animal models with high degree of predictability
- Analyse laboratory values **within** normal ranges for trends

Safety Registration : Solutions ...

- Analyse all patients with serious events in detail
- Disregard investigators´ assessments of correlation

Safety Issues (1)

QTs prolongation

- Common with macrolides and quinolones
- Ranges from a few msec to 11-12 msec
- In most patients not dangerous **but** precautions should be taken in patients with arrythmia and/or congestive heart failure and in patients on multiple drugs

Safety Issues (2)

C. difficile **Diarrhoea**

- Probably most individuals harbour *C. difficile* in the faecal flora
- Factors increasing the risk of C. difficile diarrhoea are treatment with cephalosporins, treatment with multiple drugs, esp. clindamycin combinations, high age and hospitalisation

Safety Issues (3)

Liver Toxicity

- Major problem with trovafloxacin, albeit in low frequencies
- Stopped further development of a group of MRSA-active carbapenems

Safety Issues (4)

Paediatric Use of Quinolones

- Hypothetical risk of chondrotoxicity
- Possible risk of tendon ruptures
- Probable risk of negative ecological effects since children commonly carry potential pathogens in nasopharynx (pneumococci, *H. influenzae,GABHS)*

Safety Issues (5)

Drug-Drug Interactions

- Multiple drug treatment, common (HIV, immunodeficient patients, MDR TB, etc.)
- Risk of toxicity and/or risk for decreased efficacy due to interactions increasingly common, e.g. when azole anti-fungals, HIV protease or non-nucleoside RT inhibitors, co-trimoxazole or rifampicin are used

The Gram-Negative Problem

- Gram-negative sepsis still very common; urosepsis, intraabdominal infection, OB/GYN infections, cholangitis, neonatal sepsis, infections in the neutropenic patient, etc.
- Gram-negative sepsis often fatal

The Gram-Negative Problem

- Examples of Gram-negative bacteria which are becoming increasingly resistant:
  - *Enterobacter* spp.
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumanii*
  - *Burkholderia* spp.

Antibiotics under development

Mainly Gram+ activity

- Linezolid
- Telithromycin
- Synercid
- New quinolones
- (Evernimycin)
- Daptomycin
- Etc.

Mainly Gram- activity

?

CONCLUSIONS

- Resistance a major and growing problem
- Clinical trial design needs to be refined
- High degree of safety can only be guaranteed after extensive use
- Gram-negative bacteria likely to come back with a vengeance