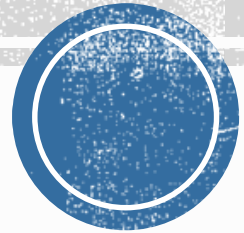
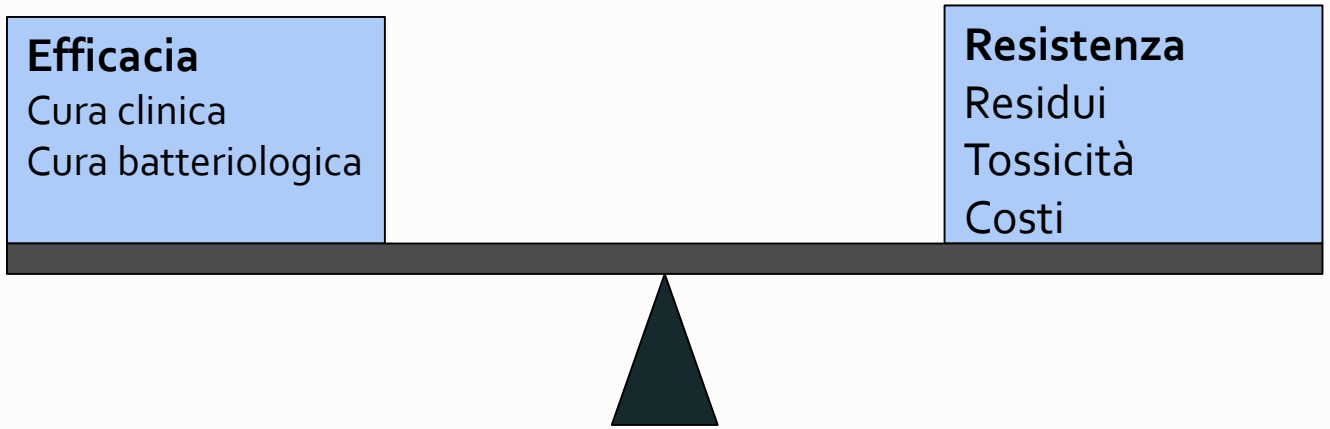
Aspetti applicativi sull'utilizzo delle linee guida nella clinica degli animali da compagnia

Ozzano dell'Emilia, 15 giugno 2018



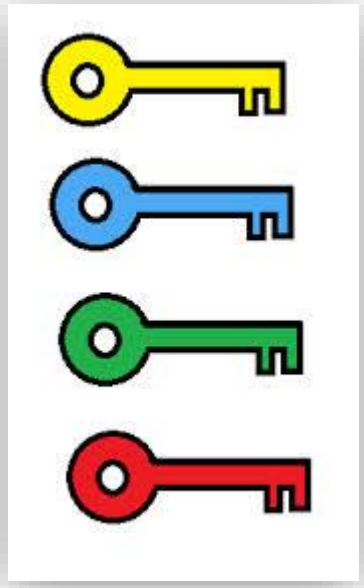
Uso responsabile dell'antibiotico

- aspettative di efficacia clinica
- bassa tossicità per l'animale
- minore influenza possibile sulla selezione di batteri resistenti



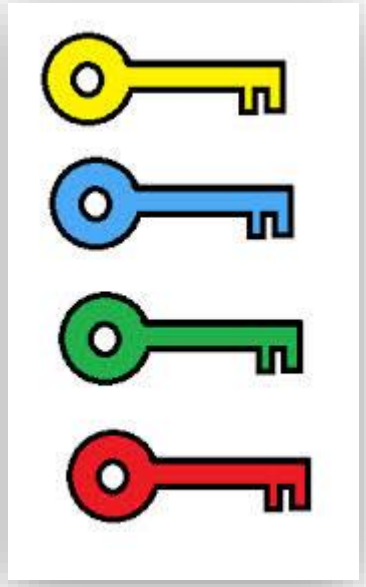
Uso responsabile dell'antibiotico

- Ottimizzare *clearance* patogeni
- "*Source control*"
- Terapia antibatterica appropriata



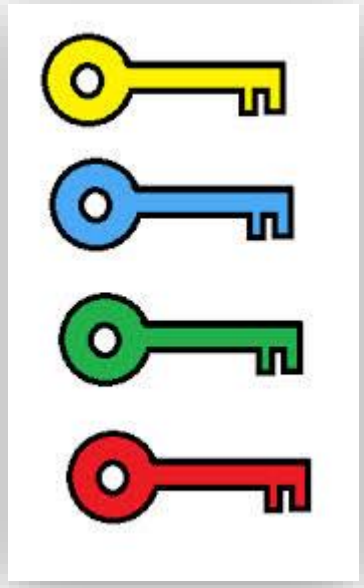
Criteri di scelta

- Paziente
- Microorganismo
- Antibiotico



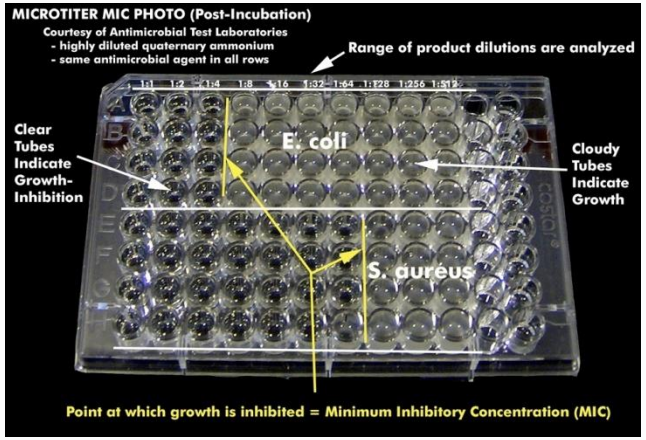
Paziente

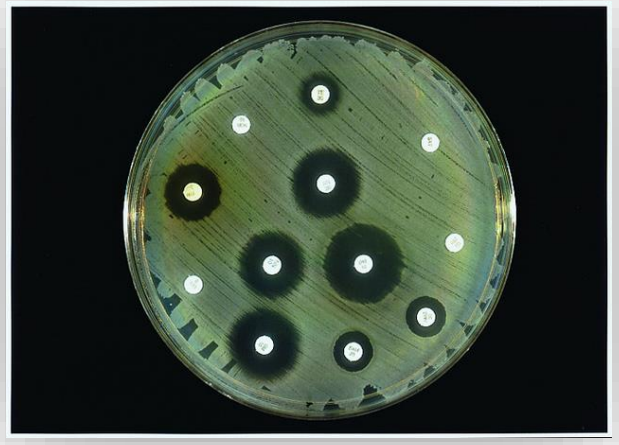
- Anamnesi: precedenti trattamenti con antibiotici
- Segnalamento
- **Stato immunitario**
- Presenza di disfunzione epatica e/o renale
- Allergie/intolleranze documentate



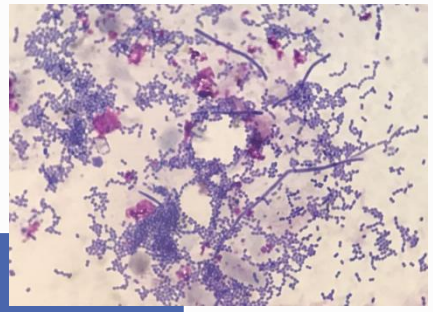
Microorganismo

- Resistenza intrinseca ad antibiotici (ad.es *Pseudomonas*-Amoxicillina)
- Resistenza locale (*Biofilm*)



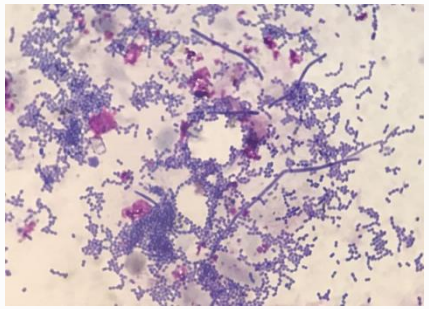


Microorganismo



Sito	Patologia	Cane %	Gatto %	Patogeni
Cavità peritoneale	Perforazione GI	35-36	47	***Staphyloccus spp., Streptococcus spp., Enterococcus spp., E. Coli, Klebsiella spp., Enterobacter spp., Pasteurella spp.***
Polmoni, cavità pleurica	Polmonite, piotorace	20	14-24	***Staphyloccus spp., Streptococcus spp., Enterococcus spp., E. Coli, Klebsiella spp., Acinetobacter spp., Pasteurella spp., Pseudomonas spp, Bordetella bronchiseptica***
Gastrointestinale	Enterite, traslocazione batterica	4	5	***E. Coli***
Riproduttore	Piometra, prostatite	25		***Streptococcus spp., Enterococcus spp., E. Coli, Klebsiella spp.,***
Tratto urinario	Pielonefrite, cistite batterica	4-10	7-8	***Streptococcus spp., Enterococcus spp., E. Coli, Acinetobacter spp.,***
Tessuti molli, Ossa	Trauma, osteomielite, ferita da morso	29	3-50	***E. Coli, Enterobacter spp***
Cardiovascolare	Endocardite		14	***Staphyloccus spp., Streptococcus spp., Enterococcus spp., Bartonella spp***

Sede infezione



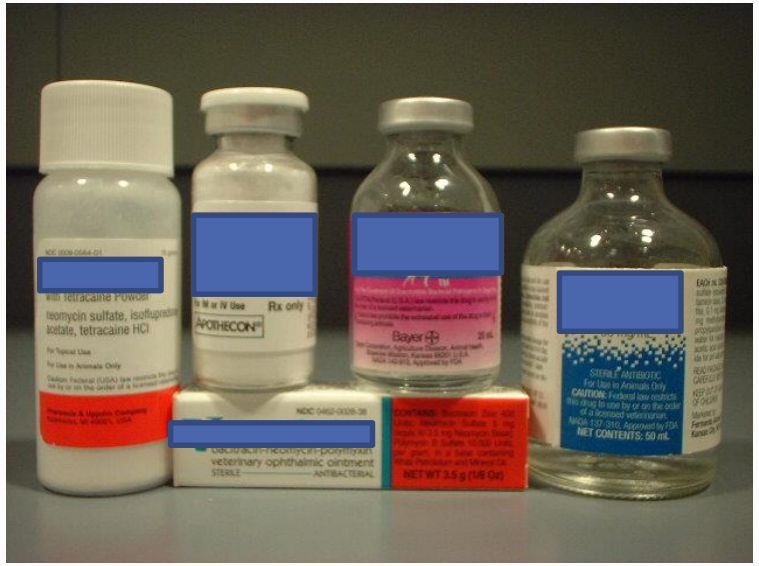
TRATTAMENTO TOPICO (cute infezioni superficiali, occhio, etc.)

TRATTAMENTO SISTEMICO: via endovenosa e muscolare da preferire

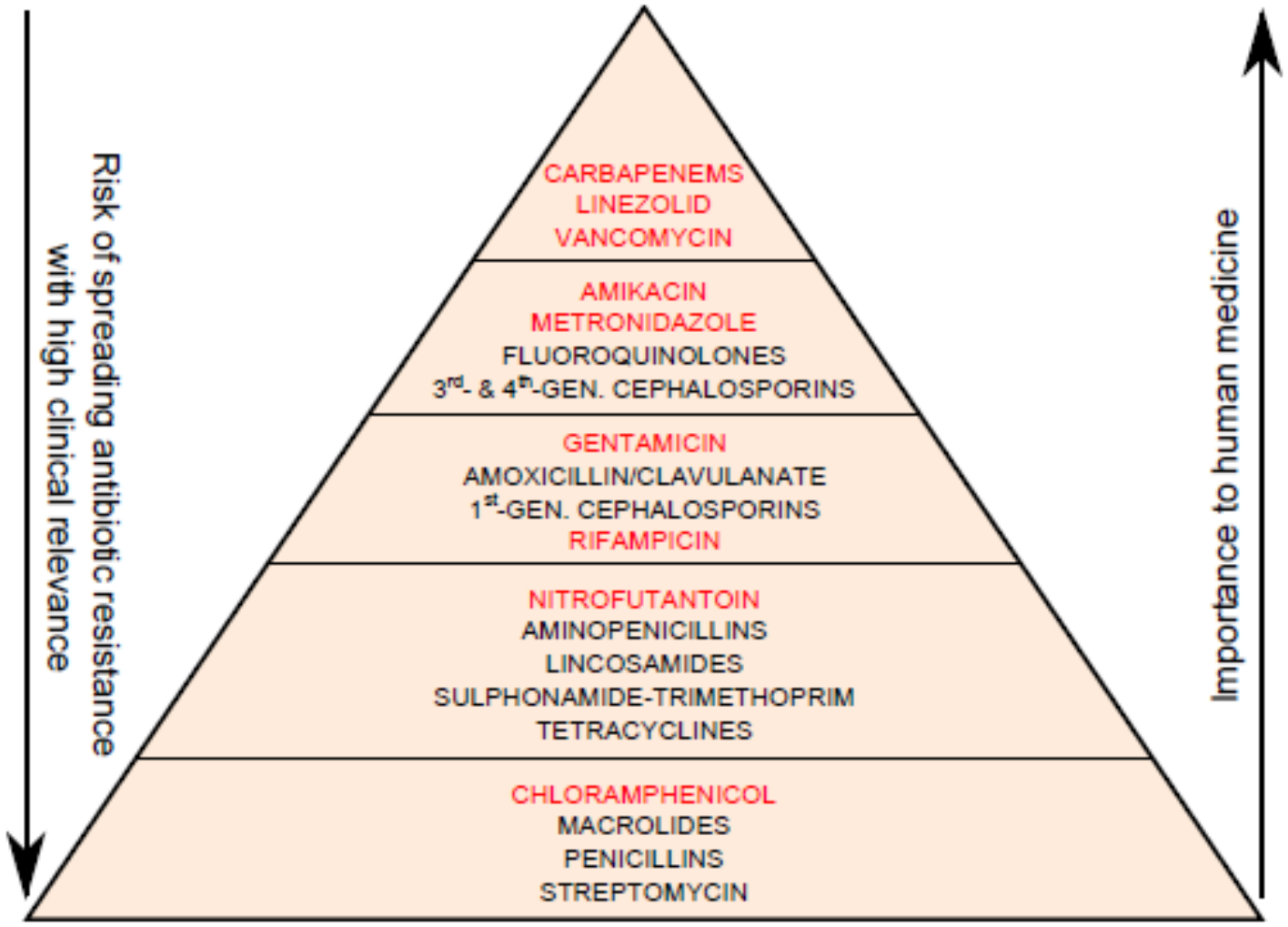
PENETRAZIONE: prostata, SNC (molecole lipofile)

Antibiotico

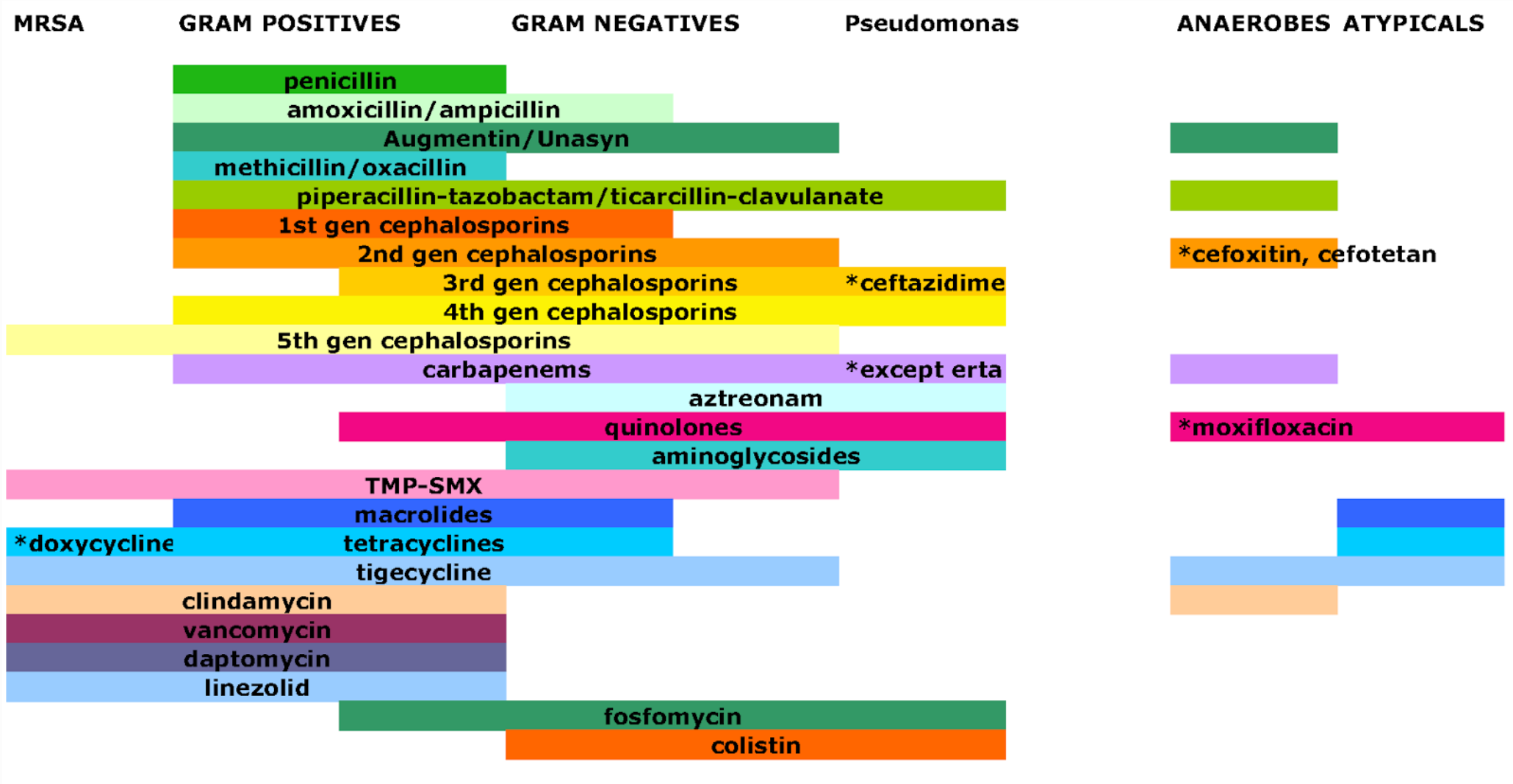
- *CIAs*
- Spettro d'azione
- PK/PD
- Tossicità
- Tempo d'intervento



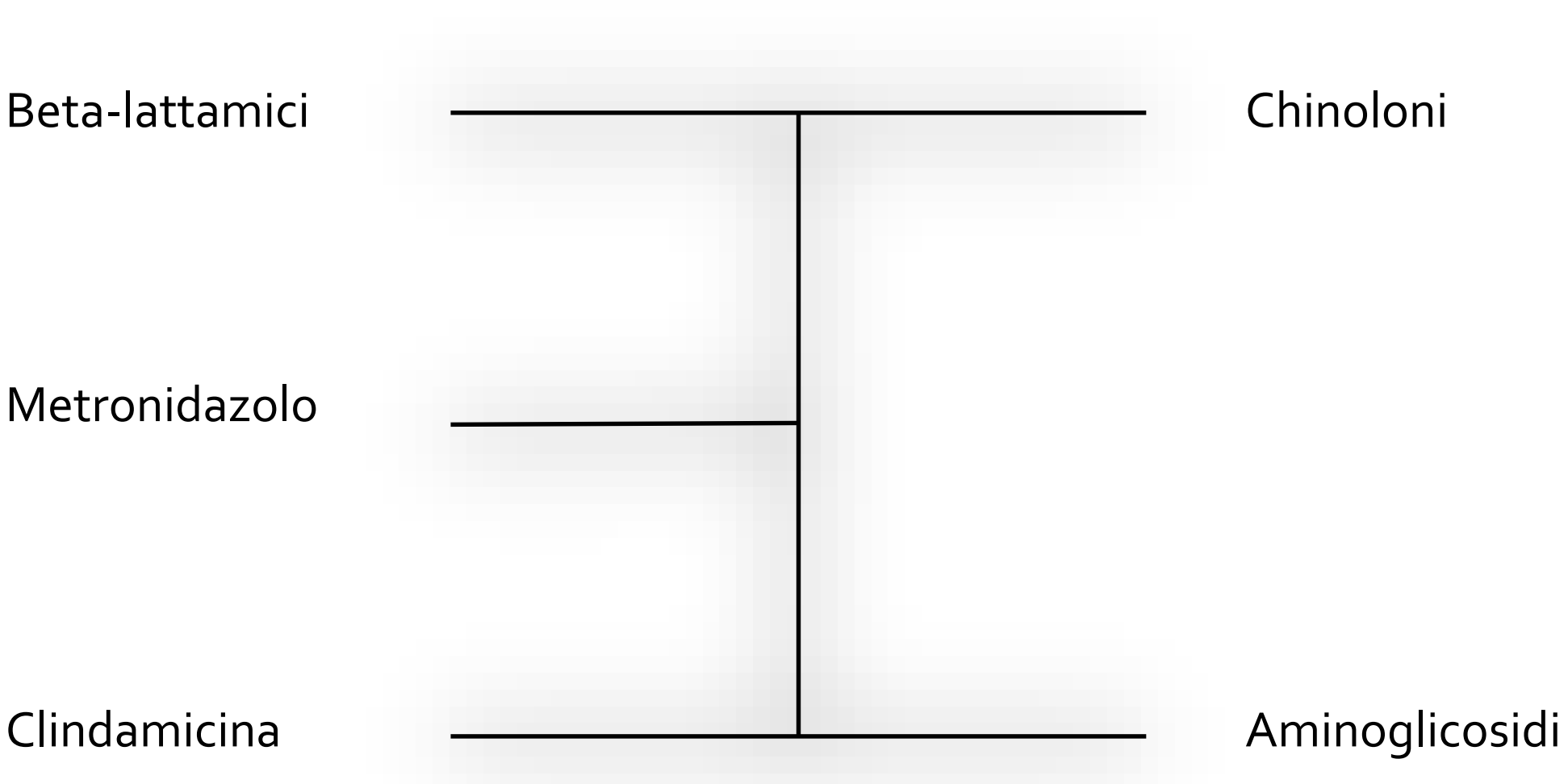
CIAs


Risk of spreading antibiotic resistance with high clinical relevance
CARBAPENEMS
LINEZOLID
VANCOMYCIN
AMIKACIN
METRONIDAZOLE
FLUOROQUINOLONES
3rd- & 4th-GEN. CEPHALOSPORINS
GENTAMICIN
AMOXICILLIN/CLAVULANATE
1st-GEN. CEPHALOSPORINS
RIFAMPICIN
NITROFUTANTOIN
AMINOPENICILLINS
LINCOSAMIDES
SULPHONAMIDE-TRIMETHOPRIM
TETRACYCLINES
CHLORAMPHENICOL
MACROLIDES
PENICILLINS
STREPTOMYCIN
Importance to human medicine

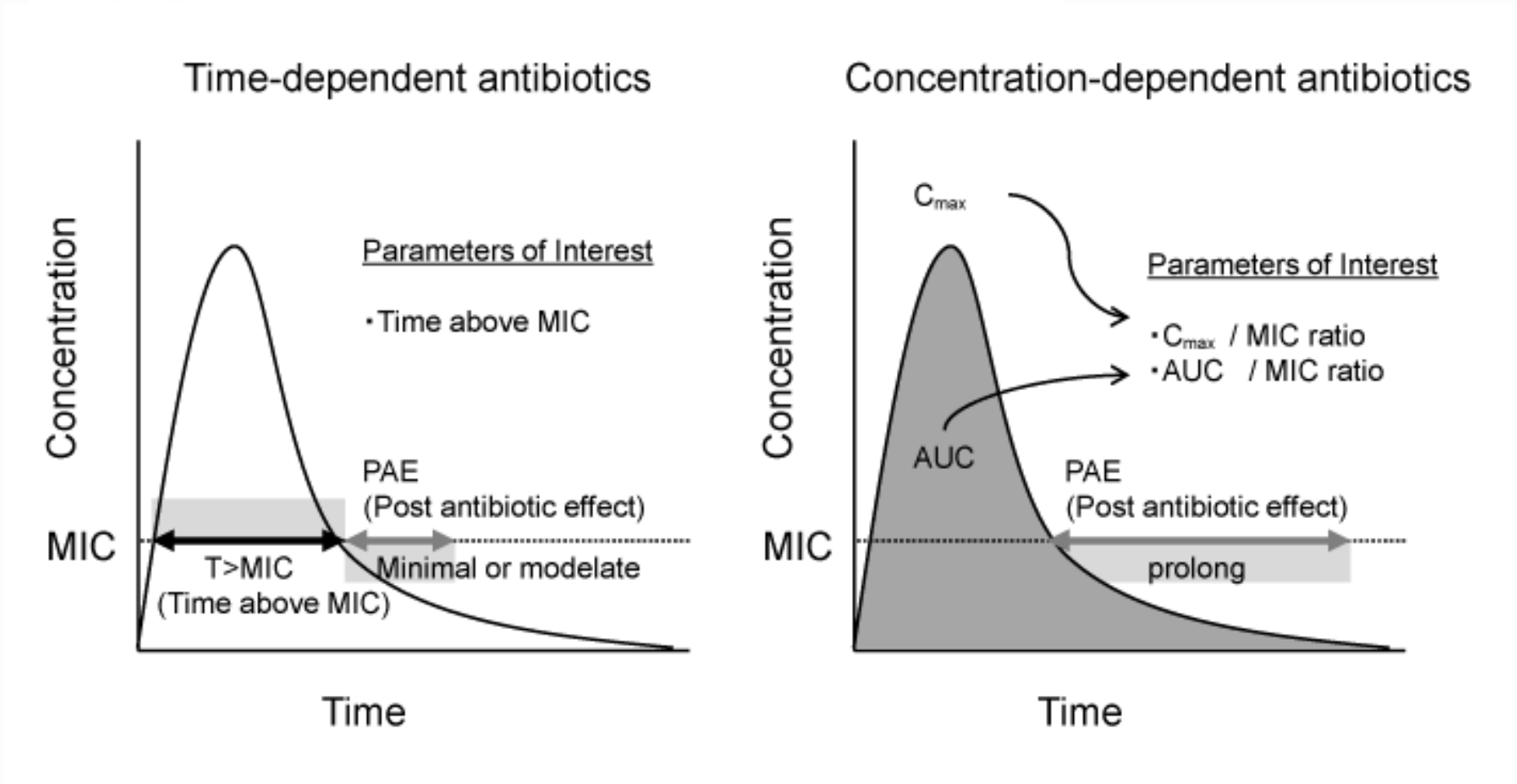
Spettro d'azione



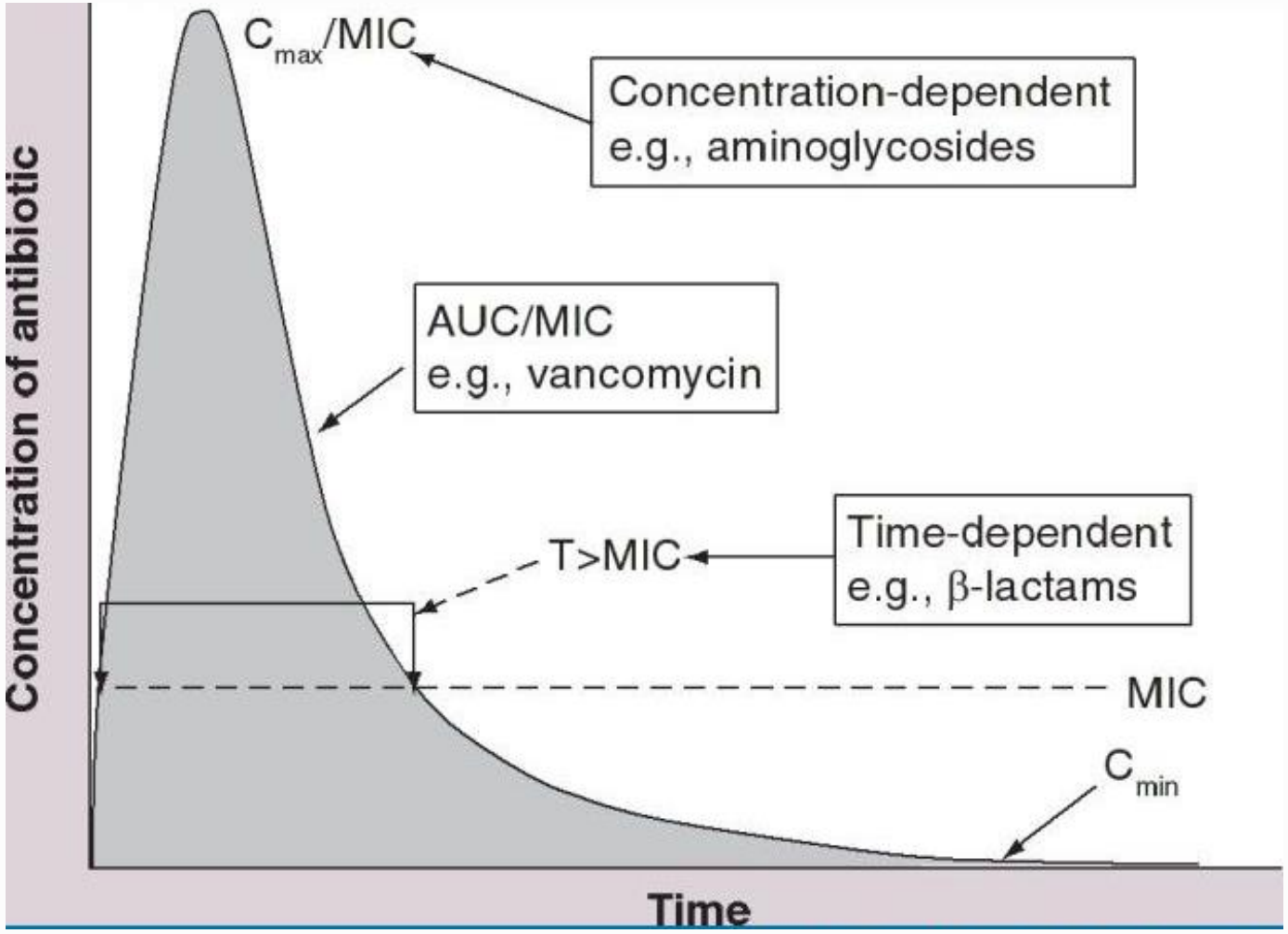
Terapia combinata



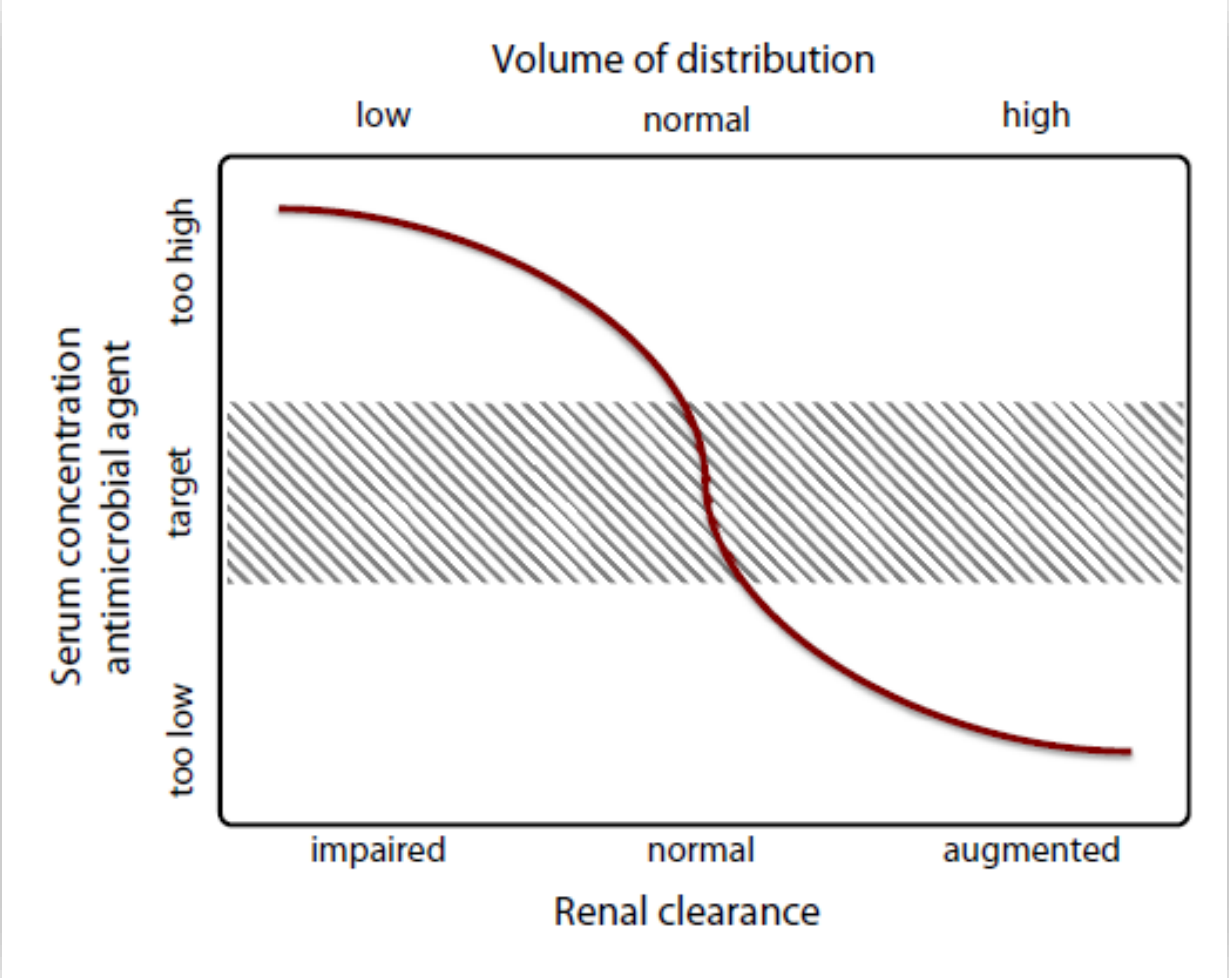
PK/PD


Time-dependent antibiotics
Concentration
MIC
Parameters of Interest
・Time above MIC
PAE
(Post antibiotic effect)
T>MIC
(Time above MIC)
Minimal or modelate
Time
Concentration-dependent antibiotics
Concentration
MIC
Cmax
Parameters of Interest
・Cmax / MIC ratio
・AUC / MIC ratio
AUC
PAE
(Post antibiotic effect)
prolong
Time

PK/PD


Concentration of antibiotic
Time
C_{max}/MIC
Concentration-dependent
e.g., aminoglycosides
AUC/MIC
e.g., vancomycin
T>MIC
Time-dependent
e.g., β-lactams
MIC
C_{min}

PK/PD

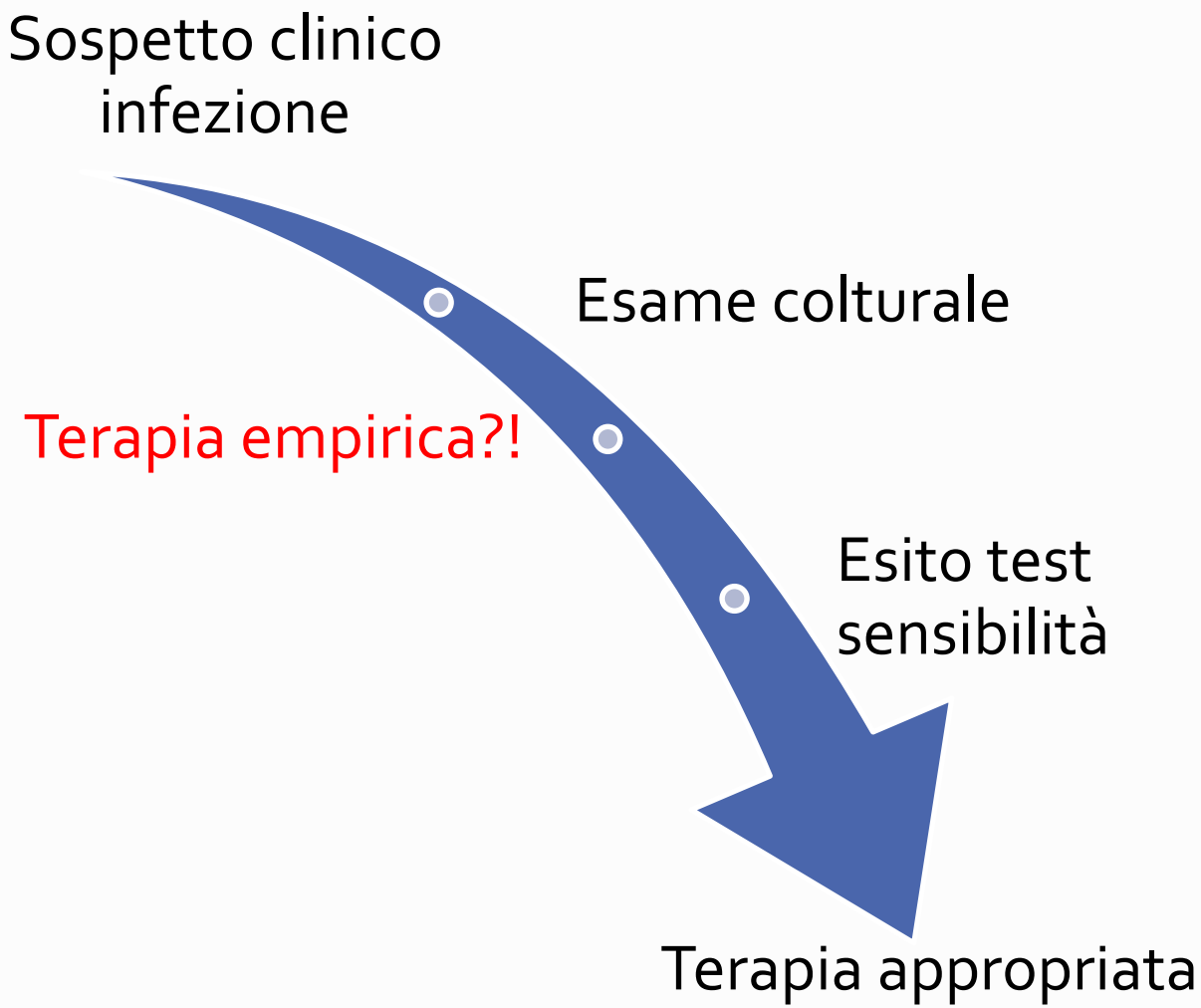

Volume of distribution
low
normal
high
Serum concentration antimicrobial agent
too high
target
too low
impaired
normal
augmented
Renal clearance

Classe	Tossicità/effetti indesiderati	Osservazioni, avvertenze e interazioni
Amminoglicosidi	Danno tubulare renale (nefrotossico) Blocco neuromuscolare Ototossicità Nistagmo	Attenzione a pazienti con malattia renale e ipovolemia/disidratazione Aumento della nefrotossicità se somministrato insieme a cefalosporine di I generazione, amfotericina-B, diuretici d'ansa e mannitolo Aumento dell'emivita in caso di insufficienza renale (Gentamicina)
β-lattamici (cefalosporine e penicilline)	Malattie immunomediate Orticaria Reazioni allergiche, soprattutto con uso parenterale Necrosi tubulare renale acuta Disturbi della coagulazione, vomito in seguito a somministrazione orale (soprattutto cefalexina)	Altri farmaci con elevato legame alle proteine (furosemide, ketoconazolo, FANS) possono competere con le cefalosporine (soprattutto cefovecina) con conseguente riduzione dell'efficacia Alcune cefalosporine possono dare reazioni false positive nella ricerca di glucosio nelle urine
Fluorochinoloni	Danno alle cartilagini articolari in animali in accrescimento Tossicità retinica nei gatti (soprattutto con enrofloxacina ad alte dosi)	I fluorochinoloni inibiscono il metabolismo di alcuni farmaci attraverso l'inibizione del CYP450 (es: teofillina, propranololo)

TOSSICITA

Tempo d'intervento

Tempo d'intervento

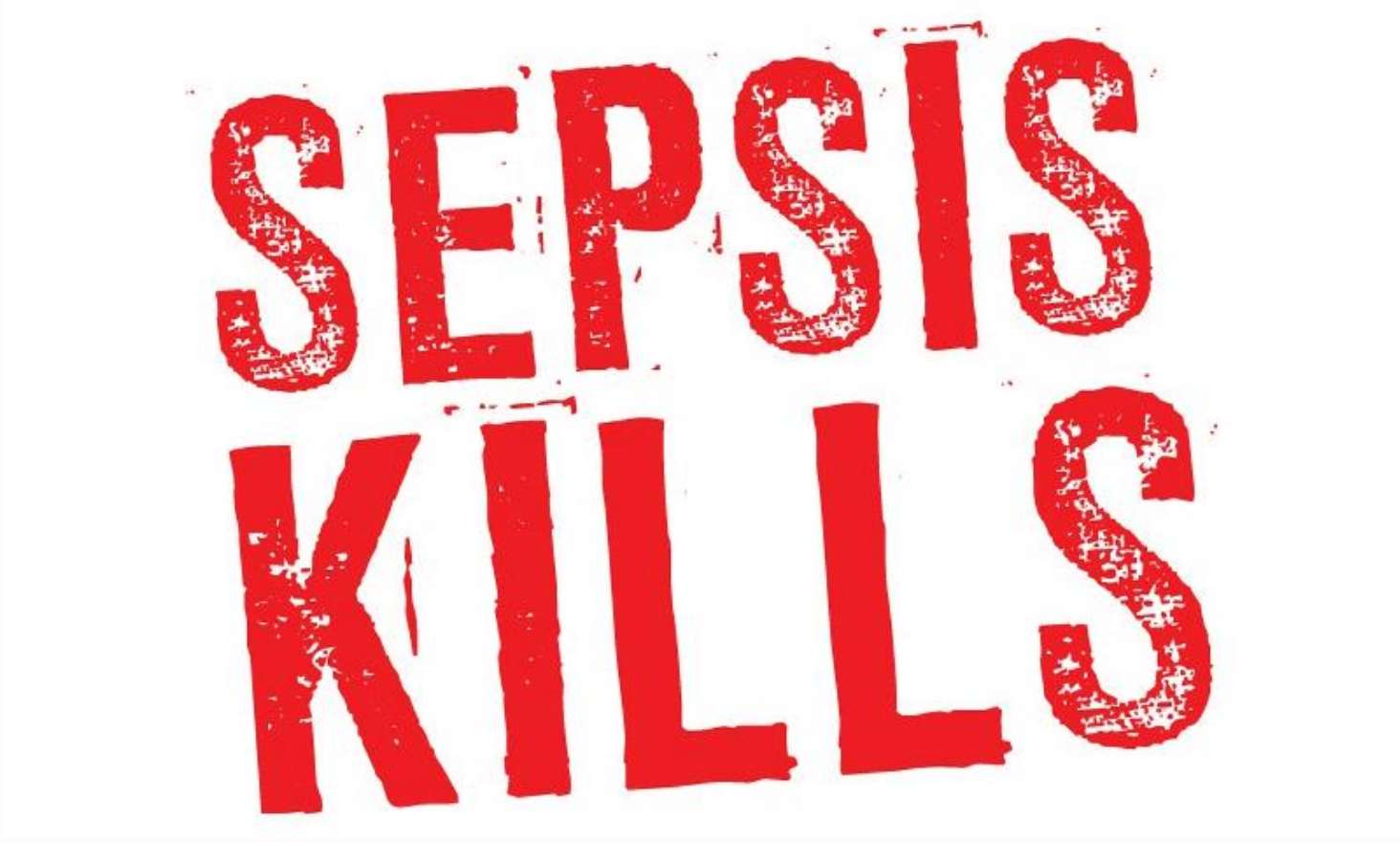


Sepsi

Elevato tasso di mortalità

Riconoscimento precoce

Trattamento tempestivo



Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

Sepsis Resuscitation Bundles

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

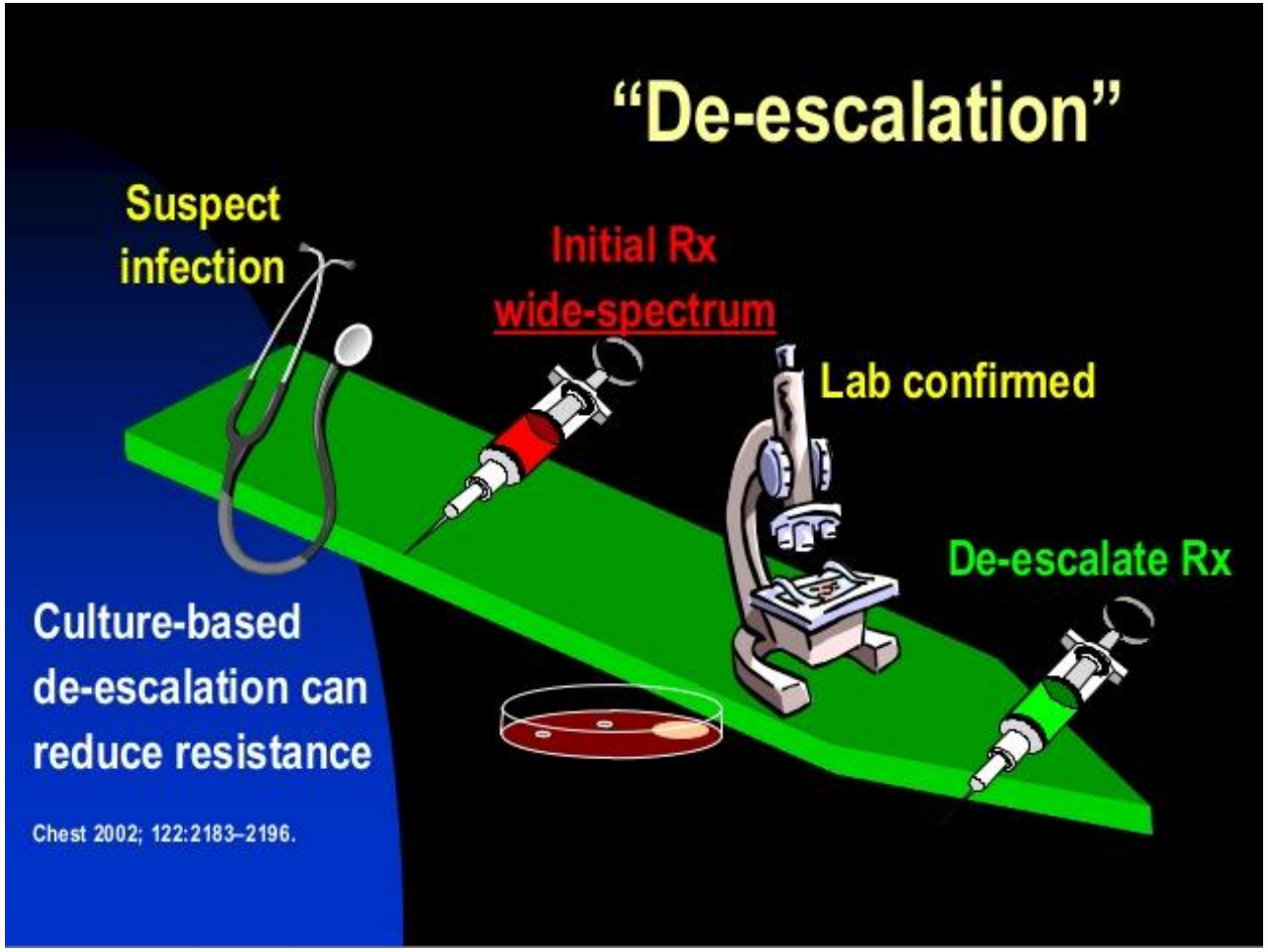
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Terapia empirica – *de-escalation*



Per quanto tempo ??

Per quanto tempo ??

- Durata insufficiente => recrudescenza dell'infezione e/o antibioticoresistenza
- Cute, prostata, tessuto osseo => trattamenti prolungati
- *Compliance* del proprietario

Per quanto tempo ??

- Scarsa evidenza in Medicina Veterinaria
- Durata breve (7 giorni) vs lunga (≥ 14 giorni)
- Controllo fonte infezione
- Stato immunitario ospite

Journal of Veterinary Internal Medicine
ACVIM
Open Access

Standard Article

J Vet Intern Med 2017;31:124–133

The Utility of Acute-Phase Proteins in the Assessment of Treatment Response in Dogs With Bacterial Pneumonia

S.J. Viitanen, A.K. Lappalainen, M.B. Christensen, S. Sankari, and M.M. Rajamäki

Durata terapia antibatterica sulla base di proteina C-reattiva:

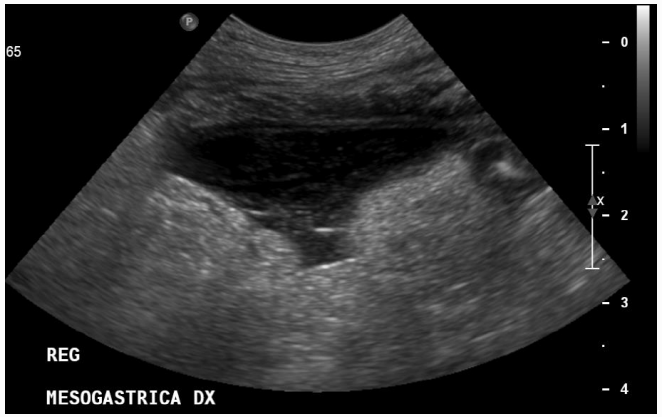
Durata del trattamento significativamente ridotta

No aumento delle recidive rispetto a terapia standard

Cane meticcio M 2 anni " Einstein"

- Post operatorio peritonite settica da c.e.
- Già in terapia antibatterica da alcuni giorni

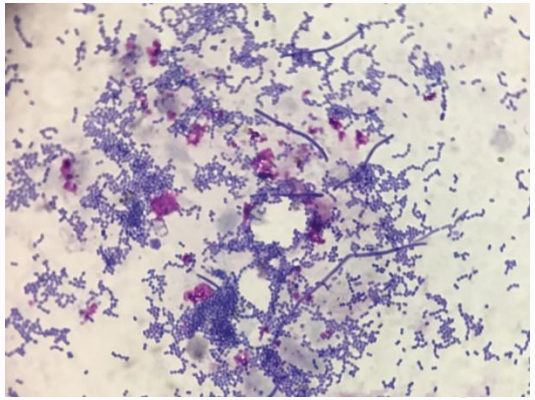
TERAPIA EMPIRICA PRE-OP



- Ampicillina-sulbactam: 22 mg/kg ev TID
- Marbofloxacin: 4 mg/kg ev SID

Esame colturale: *Escherichia coli (+++)* + *Enterobacter cloacae (+++++)*

.....antibiogramma.....



Cane meticcio M 2 anni " Einstein"

Positivo per	Enterobacter cloacae (+++++)
Sensibile a	Amikacina
	Imipenen
	Sensibile anche a: Cefepime
Positivo per	Escherichia coli (+++)
Sensibile a	Amikacina
	Ciprofloxacina
	Cloramfenicolo
	Doxiciclina
	Gentamicina
	Imipenen
	Marbofloxacina
	Tetraciclina
	Trimethoprim/sulfa
	Sensibile anche a: Cefepime e Minociclina

Journal of Veterinary Emergency and Critical Care **25**(1) 2015, pp 152–159

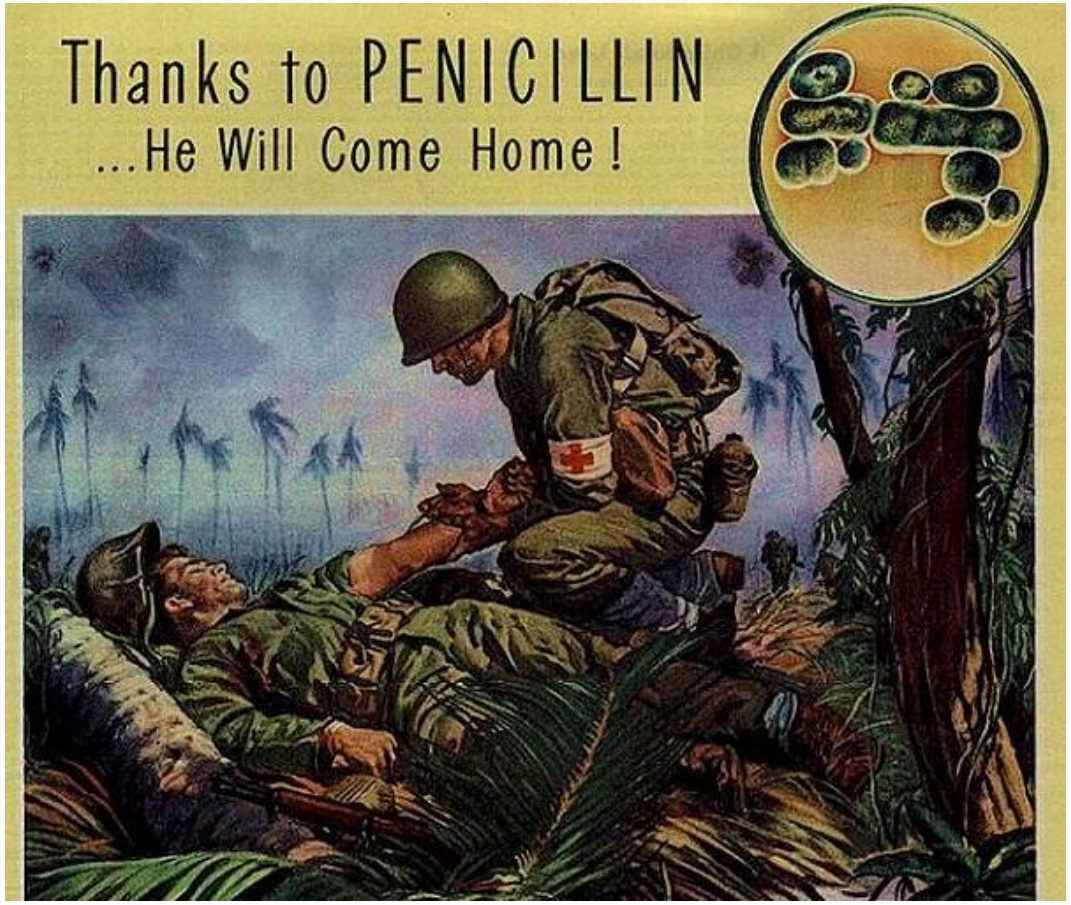
Impact of appropriate empirical antimicrobial therapy on outcome of dogs with septic peritonitis

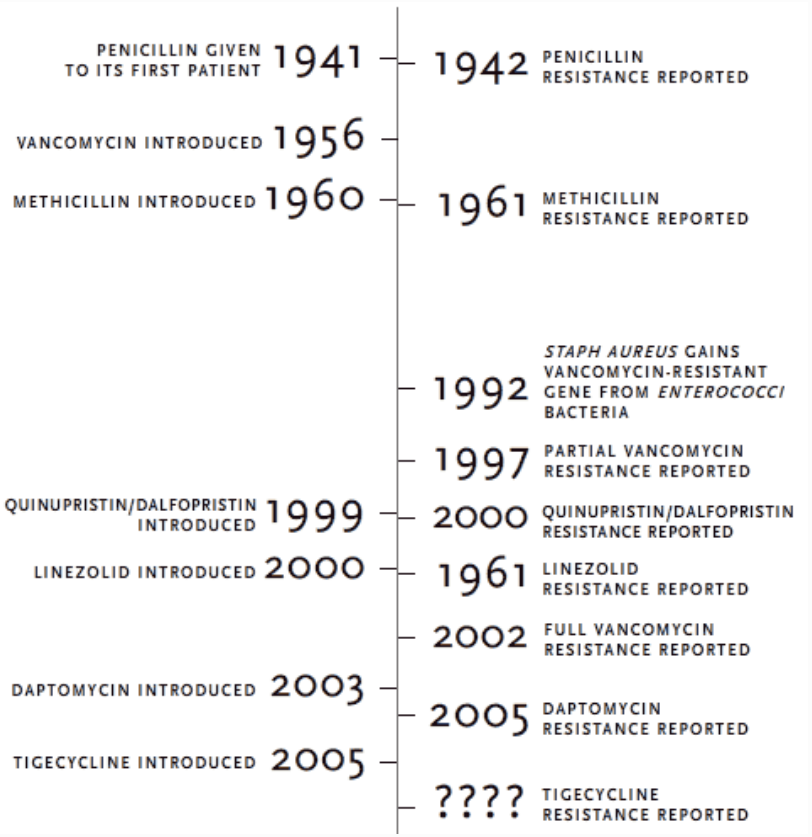
Amy E. Dickinson, DVM, DACVECC; Jennifer F. Summers, BVetMed, MSc; Jamie Wignal, BVetMed, DACVS; Amanda K. Boag, MA, VetMB, DACVIM, DACVECC, DECVECC and Iain Keir, BVMS, DACVECC

Terapia antibatterica inappropriata in ~ 50 % dei pazienti

- precedente terapia antibatterica (30 giorni)
- precedente chirurgia addominale (30 giorni)

Antibioticoresistenza





MAC

Saturday Review

JANUARY 3, 1959 / 25¢

SR/RESEARCH
SCIENCE & HUMANITY

DOCTORS AND ANTIBIOTICS

Taking the Miracle Out of Miracle Drugs

By John Lear

Arthur Schlesinger, Jr. author of "The Coming of the New Deal." ►

(See Page 15)

THE ROAD TO BERLIN

An Editorial

TAKING THE MIRACLE OUT OF THE MIRACLE DRUGS

PRESCRIPTION of antibiotics without a specific cause for such treatment has reached disturbing proportions. The practice has been discussed in medical journals, and some of the profession's discomfiture has leaked to a wider public. But no general, full disclosures have been made. I shall therefore begin by calling attention to a plainly worded censure published in the October 1958 issue of *Postgraduate Medicine*. Dr. C. Henry Kempe, professor of pediatrics and head of the department of pediatrics at the University of Colorado Medical School in Denver, couched the rebuke in language that might ordinarily be expected to be reserved for the instruction of healers from some bypassed culture.

"It is suggested," he wrote, "that (the physician) . . . formulate a tentative specific . . . diagnosis . . . *prior* to the administration (of an antibiotic) . . . and that he give such a drug only when (its effectiveness is) . . . indicated (by the diagnosis)."

In italicising the word *prior*, Dr. Kempe expressed an extraordinary need for emphasis. Why is such a pointed exhortation called for in these days when the rawest medical student is assumed to accept the primacy of accurate diagnosis? Dr. Kempe offered this explanation:

"All of us desire to get our patients well as quickly as possible and all of us desire to be completely up to date and therefore we are usually tempted to try everything new as fast as it comes along. . . . We quickly make . . . new antibiotics . . . useless to us by their overuse . . . as forms of better aspirin . . . in the treatment of fever . . . rather than what they truly are. We constantly assume that a drug is no good if the fever fails to drop promptly, and this leads to the quick addition of a second and a third antibiotic."

He plainly felt that many of his fellow physicians had forgot another beginner's lesson in medicine:

"Fever is only a symptom . . . a symptom of many diseases *other* than bacterial infections . . . a prominent symptom in viral respiratory infections which are insusceptible to antibiotic treatment at present."

The injunction was clear. Distinction must be drawn between those fevers which antibiotics unquestionably are effective in lowering (and in these, which tend to be the historic plagues of man—typhus, typhoid, meningitis, syphilis, gonorrhea, tularemia, brucellosis, bacterial endocarditis, pneumonia, tuberculosis, scarlet fever, intestinal disorders, and boils—the effect is miracle-like) and other fevers where antibiotics are not only useless but a potential danger.

An antibiotic is by definition a potion made by a living organism (like the one pictured at work on our masthead above) to kill or disable another living organism. This type of drug is useful principally against diseases caused by bacteria, germs, microscopic "bugs." Virus infections are susceptible in some cases: trachoma, "parrot fever," and the social disease known as *lymphogranulomia venereum*, for instance. Some diseases caused by the virus-like *rickettsia* (typhus, scrub typhus, Rocky Mountain spotted fever are examples) also respond to antibiotic treatment. But antibiotic prescriptions are an extravagant waste of money if they are directed against any of the commonly recognized virus ills, such as infantile paralysis, encephalitis, influenza, or the common cold.

By failing to distinguish between one fever and another before prescribing antibiotics, Dr. Kempe warned, physicians have confronted themselves with "the problem of no longer knowing the natural history of many diseases"—the changed environment of the originating organisms, their population distribution, their identifying characteristics. In short, doctors are in danger of forgetting how to tell common sicknesses apart. Should that happen, modern medicine would succumb to mumbo-jumbo.

There is time to avert castastrophe by reversing the trend. Until the prevailing carelessness is brought to an end, however, individual calamities can and will pile up as a result of indiscriminate antibiotic dosing. In summing up the situation in *Postgraduate Medicine*, Dr. Kempe listed five areas pregnant with the probability of tragedy.

First—and worst on his list was the masking of serious disease by ineffective medication. The real cause of an undiagnosed infection does not appear for five to ten days after the first visit to the doctor. It takes that long to decide that an antibiotic isn't working. During the interval of ignorance, the patient is getting no better and is probably getting worse. In absence of specific diagnosis, other alternatives may be presenting themselves, such as

Second—vomiting, nausea, diarrhea, anal itching due to poisoning;

Third—hypersensitivity to antibiotics, resulting in various forms of distress from outbreaks of hives to death in extreme cases;

Fourth—alteration of the normal balance of bacteria in the digestive system, bringing on dangerous complications, or;

Fattori di rischio

- Consumo antibiotici
- Precedenti trattamenti antibiotici
- Scarse misure igienico-sanitarie/controllo infezioni
- Tempi Ospedalizzazione/ICU
- Ventilazione meccanica

Antibiotici e Resistenze

Table 1.1: Antibiotic resistance in clinical *Staphylococcus pseudintermedius* isolates from companion animals in Denmark and Sweden.

Antibiotic	Denmark 2000-2005 (n=201)[a]	Denmark 2011-2012 (n=318)[b]	Sweden 2011 (n=388)[c]
Amoxicillin/clavulanate	0%	10%	-
Oxacillin	-	3%[d]	2%[d]
Cefalotin	<1%	6%[e]	2%
Erythromycin	30%	29%	30%
Clindamycin	27%	30%	24%
Chloramphenicol	13%	14%	-
Tetracycline	24%	0%[f]	26%
Gentamicin	-	4%	2%
Amikacin	-	4%	-
Enrofloxacin	1%	3%	2%[g]
Marbofloxacin	-	3%	-
Sulfamethoxazole/ trimethoprim	3%	4%	6%

Development of antimicrobial drug resistance in rectal *Escherichia coli* isolates from dogs hospitalized in an intensive care unit

Jennifer Ogeer-Gyles, DVM, MSc; Karol A. Mathews, DVM, DVSc, DACVECC; William Sears, MSc; John F. Prescott, VetMB, PhD; J. S. Weese, DVM, DVSc, DACVIM; Patrick Boerlin, Dr Med Vet, MSc

Antimicrobial agent	Percentage of isolates resistant				*P* value*	OR† (95% CI)
	Day 0 (n = 155)	Day 3 (169)	Day 6 (74)	Day 9 (15)		
Ampicillin	20.6	46.1	67.6	86.7	< 0.001	2.6 (1.7–3.8)
Cephalothin	53.5	56.8	59.5	86.7	0.225	1.1 (0.9–1.4)
Amoxicillin-clavulanate	15.5	22.5	44.6	33.3	0.012	1.6 (1.1–2.2)
Tetracycline	16.1	16.6	27.0	20.0	0.394	1.2 (0.6–1.8)
Ceftiofur	11.6	11.8	10.8	0.00	0.902	1.0 (0.6–1.8)
Cefotaxime	12.3	12.4	10.8	0.00	0.913	1.1 (0.3–3.7)
Cefoxitin	12.3	11.8	13.5	0.00	0.799	1.1 (0.6–1.8)
Gentamicin	5.8	5.9	0.0	0.00	1.000	NA
Chloramphenicol	10.3	17.8	16.2	40.0	0.191	1.4 (0.8–2.5)
Enrofloxacin	9.7	18.9	21.6	33.3	0.053	1.7 (1.0–3.0)
Nalidixic acid	9.7	21.3	21.6	33.3	0.029	2.0 (1.1–3.8)
Trimethoprim-sulfamethoxazole	5.2	15.4	20.3	0.0	0.197	1.4 (0.8–2.2)
Ampicillin or cephalothin	55.5	68.6	78.4	93.3	0.003	1.5 (1.2–2.1)
Ampicillin, cephalothin, or amoxicillin-clavulanate	55.5	68.6	78.4	93.3	0.003	1.5 (1.2–2.1)
Enrofloxacin or nalidixic acid	9.7	21.9	21.6	33.3	0.043	1.8 (1.0–3.1)

**P* value for a test for a linear trend in prevalence of resistance over time. †Odds ratio is the increased likelihood of antimicrobial resistance developing on day 9, compared with day 0, for the antimicrobial agent or groups of antimicrobial agents.
NA = Not applicable.

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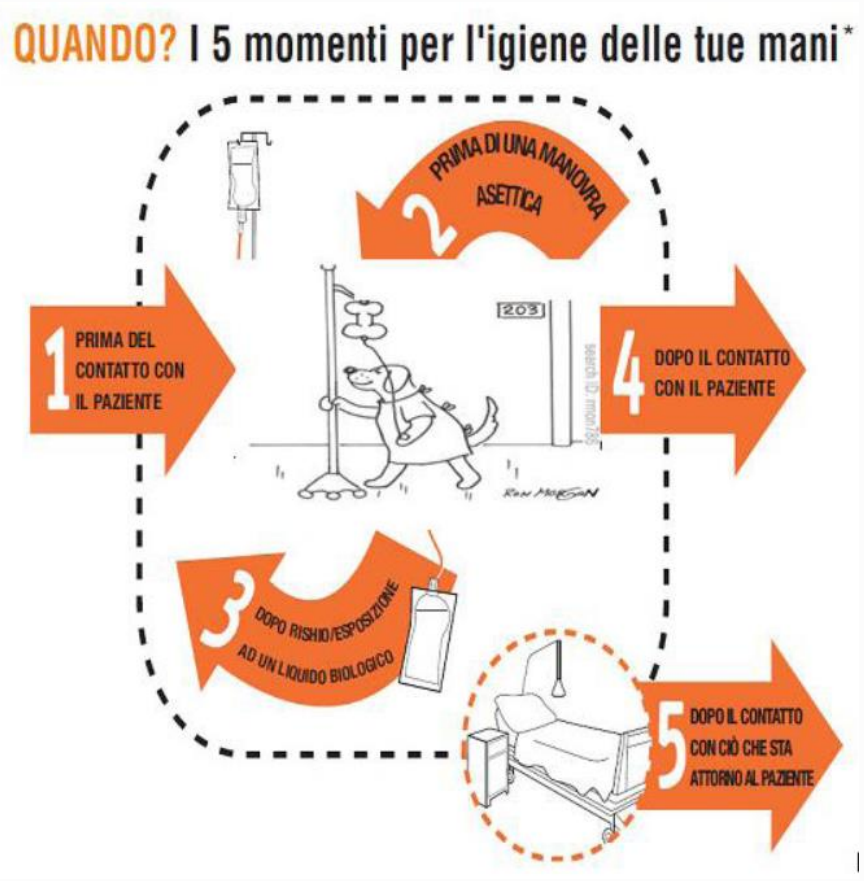
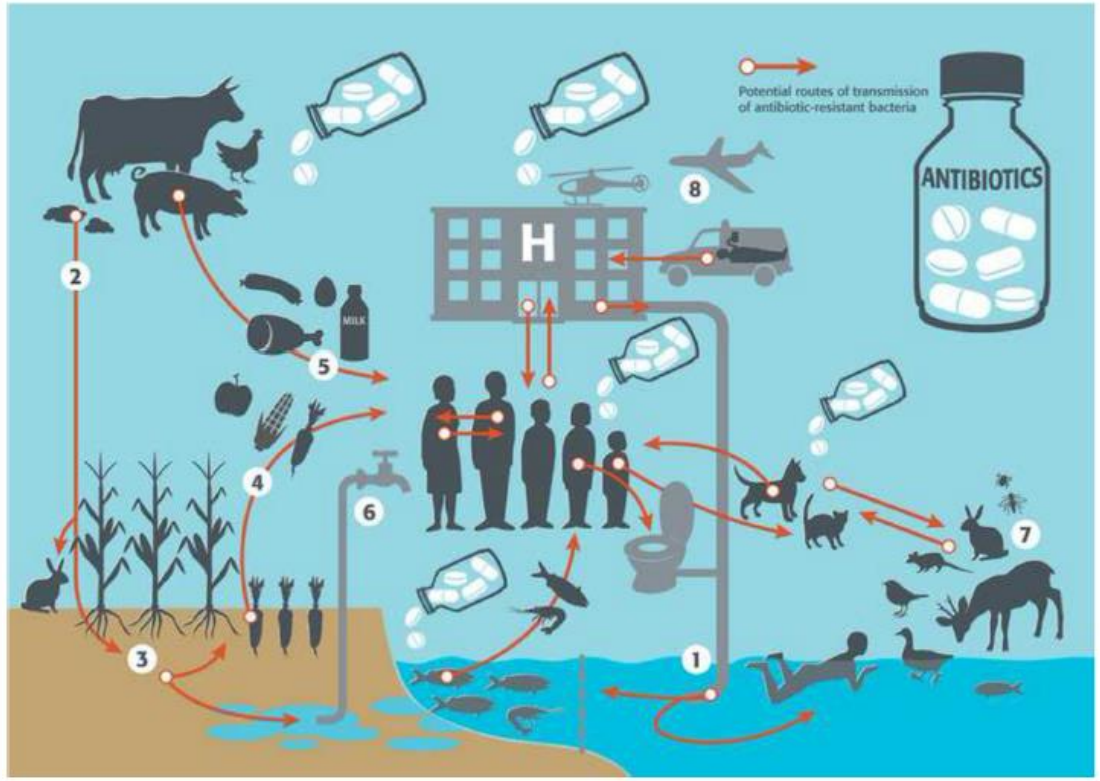
«Clean Care, Safe Care»



Conclusioni

- Uso appropriato antibiotici
- Esami colturali e test di sensibilità
- Controllo infezioni
- Misure preventive



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