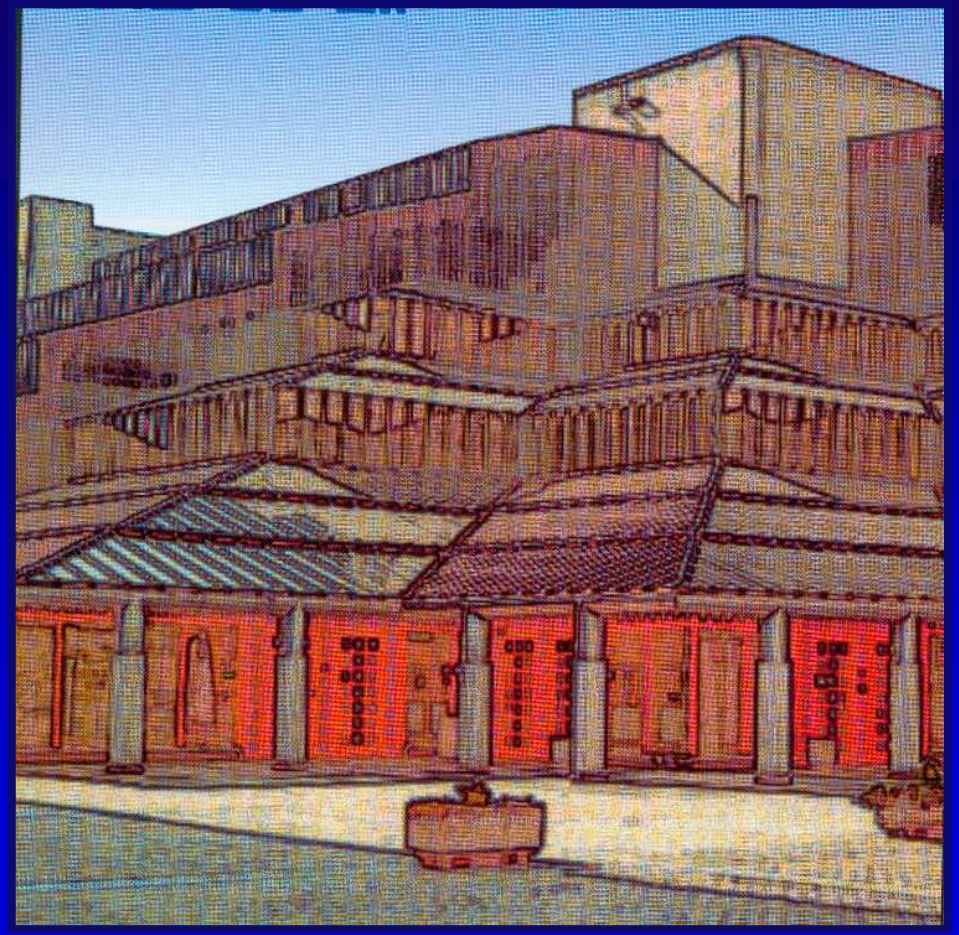
RESISTANCE TESTING CHALLENGES AND SOLUTIONS WITH EMPHASIS ON PATIENT CARE



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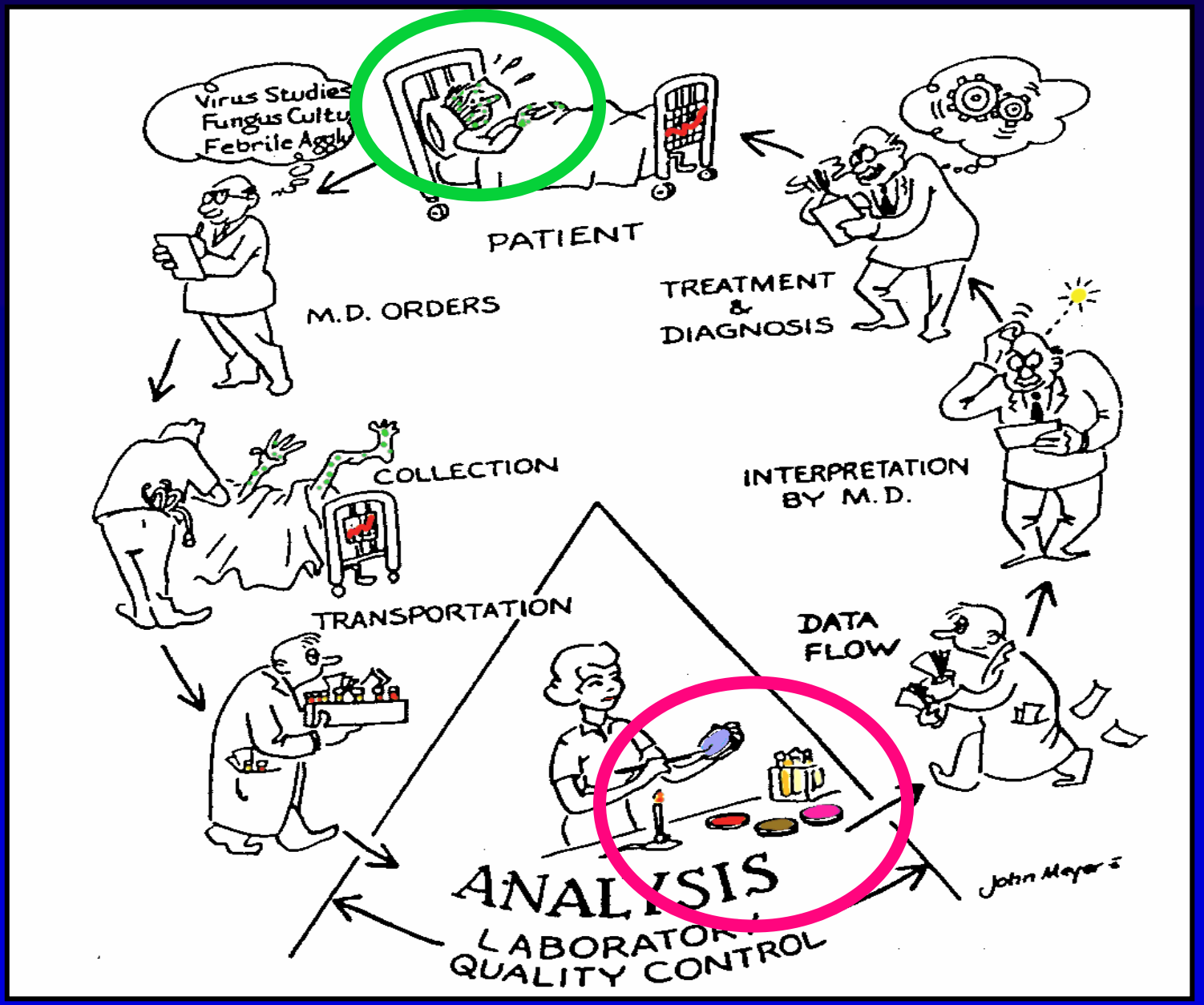

Virus Studies
Fungus Cultu
Febrile Aggl
PATIENT
M.D. ORDERS
TREATMENT
&
DIAGNOSIS
COLLECTION
INTERPRETATION
BY M.D.
TRANSPORTATION
DATA
FLOW
ANALYSIS
LABORATOR
QUALITY CONTROL
John Mayer

Clinical Microbiology Laboratories Current Challenges

Specimen collection

Specimen Analysis : Relevant Pathogens

Identification AST

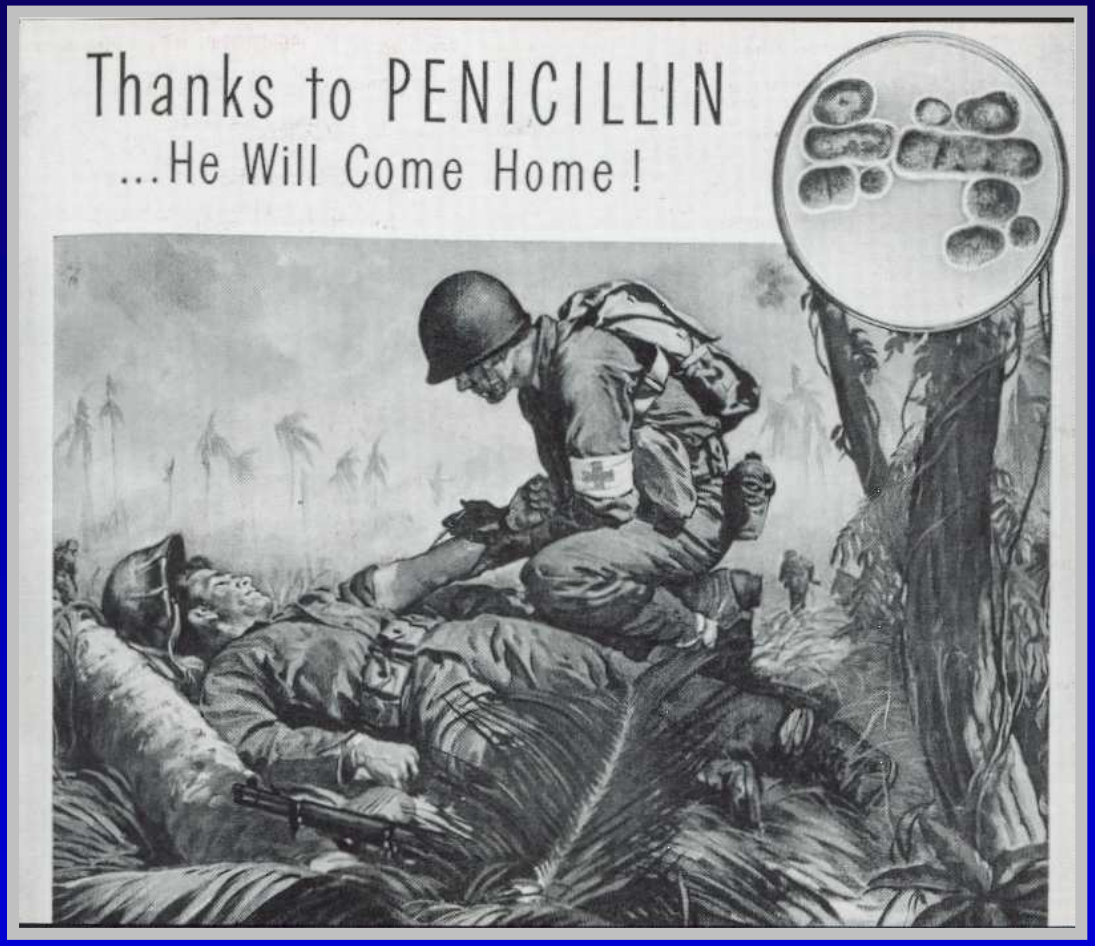
Patient's optimized management

RESISTANCE:

- Detection / method-dependant
- Level of in vitro expression
- Predictive value
- Microbiological & therapeutic interpretations

Cost effective & timely
Decreasing resources !

A few years of wonder and then …



INCREASE OF FAILURES

Very high levels of Resistance

emergence + spread + escalation

« Difficult to treat » patients

Some of the XXIst century-Challenges in infectious diseases

- Microorganisms
  - Increasing antimicrobial Resistance
  - Resistance determinant
  - « Pathogens » evolution
- Patients and medical improvements
  - Critical care
  - Immuno-compromised
  - Nosocomial infections

The challenging pathogens

In hospital

- *S. aureus* (MRSA, GISA, VRSA)
- *Enterococci* (GRE)
- *Enterobacteriaceae* (ESBL, carbapenemase, FQ)
- MDR-*P. aeruginosa*
- MDR-*Acinobacter baumanii*

In community

- MDR-*S. pneumoniae*
- CA-MRSA
- *Salmonella* (ESBL, FQ)
- *Campylobacter* (FQ, macrolides)
- Helicobacter pylori
- MDR-*M. tuberculosis*

Appropriate therapy saves lives

- Early inappropriate therapy
  - *Increase of mortality in severe infection*
- Infection with antibiotic-R bacteria
  - *Increase of risk of inappropriate therapy*
- Antibiotic-R organisms
  - *More commonly associated with inadequate therapy*
- Streamlining therapy to narrow spectrum drug
  - *Saving costs*

Weinstein et al. Clin Infect Dis 1997:24:584
Kollef et al Clin Infect Dis 2000: 31 (suppl. 4): S131

Appropriate therapy saves lives

- **Target empiric therapy** to likely pathogens,
  - based on hospital, regional, specific epidemiology.
- **Target definitive therapy** to known pathogens,
  - based on accurate, quantitative S results

Who / What do we treat ?

- Patient ?
- Disease ?
- Bug ?

Main goals of anti-infective therapy

- Clinical cure of patients
- Eradicating the pathogens
- To avoid development of resistance
- To avoid transmission

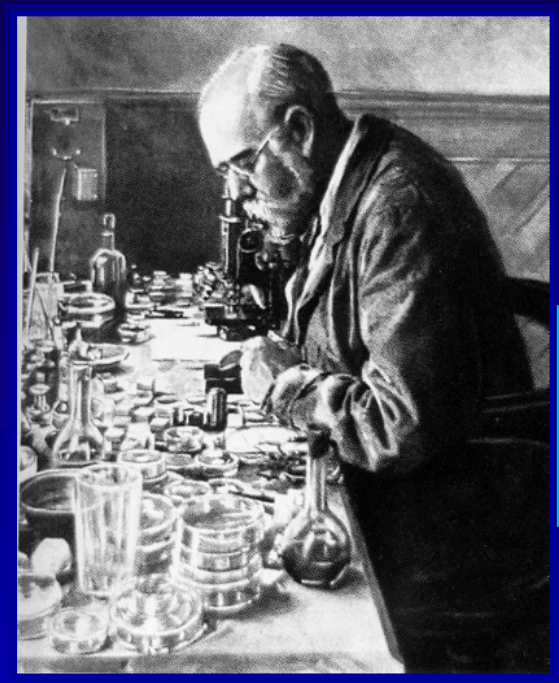
By giving « supposedly » or proven effective antibiotic

Choices often based on results in terms of « S » or « Non S »

SIR, bacteria are not simply « S » or « Non S »

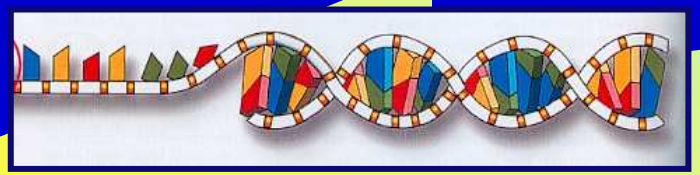
S

- Varies over a wide range
- May be quantified by MIC
- May result in overdosing or underdosing
  - Risk of R development
  - Unnecessary costs
  - Increase morbidity/mortality
- Standard definition of Resistance



ACCURATE DETECTION of clinically & epidemiologically significant R-determinants

COST-EFFECTIVE to patient care & infection control



Are AST results clinically relevant & reliable ?
Therapeutic predictive values

- Many variables affecting results
  - Standardization
  - *In vitro // in vivo ?*
- Current breakpoints
  - S, I, R
    - NCCLS, BSAC, SFM, Japanese, ….

Different interpretative criteria

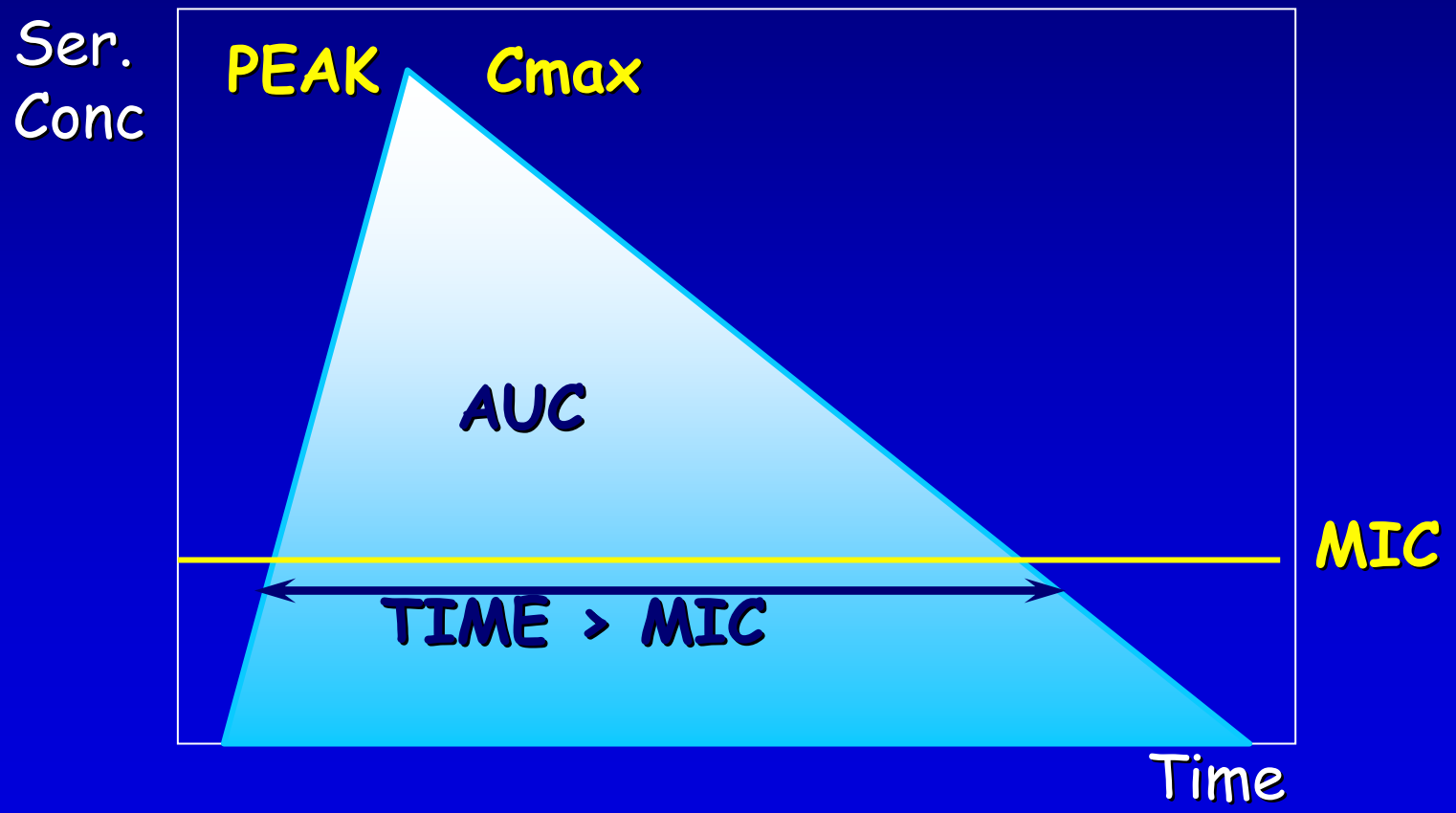
P.aeruginosa ATCC 27853, same MIC yet different categories

Are AST results clinically relevant - reliable ?
Therapeutic predictive value

- Many variables affecting results
  - Standardization / *in vivo ?*
- Current breakpoints
  - S, I, R
    - NCCLS, BSAC, SFM, Japanese, ….
  - Safety or efficacy ?
  - Evolution *// pharmacology-pharmacodynamics ?*
    - *β-lactams, aminoglycosides, FQ*
- Expression of resistance? Detection ?

ART *vs.* AST

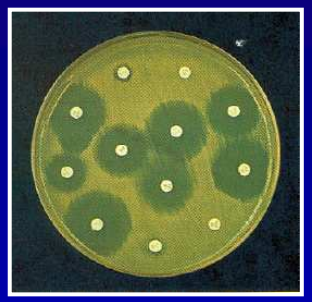
MIC determinations and PK/PD model



Practical recommendations for PK/PD -optimized therapy

Drug class	Recommendations
B-lactams	-remain > MIC for at least 50 % of the time
	-Fractionate the dose
Aminoglycosides	-Obtain Cmax/MIC ratio of at least 8
	-Administer once daily
Fluoroquinolones	-Obtain a 24-H AUC/MIC ratio > 125
	-Obtain Cmax/MIC ratio of at least 8
	-Do not overfractionate the daily dose
	-Consider lowering breakpoints for older FQ
Etc.	

AST methods routinely used in Belgium (*E.faecium* EQC-ISP 2003)



- « Disk » diffusion
  - Paper discs 25 %
  - Rosco tablets 50 %
- « MIC » Automated system
  - Vitek 1 7.5 %
  - Vitek 2 17 %
- Real MIC Etest
  - Vancomycin 25 %

AST methods routinely used

	D.Diffusion	Vitek/Phoenix	E test
Results	S, I, R	« MIC »	Real MIC
Cost (Invest./fct)	Low/Low	High/high	Low/very high
Flexibility	++	-	++
Pro & Contra	Not for fastidious, …	Workload, TAT, quality	All kinds of organisms, even slow growing
	False S	Reproducibility	Large range of MICs
	// Breakpoints	Sofware expert	Time consuming
		Not for +/- fastidious, …	
		Black box	
		R expression ?	
		Limited range of MICs	

To prevent antimicrobial R = to treat infections effectively

- Detection of Resistance
- Target optimal therapy
  - Choice of the most potent drug in class
  - Giving optimal regimen
    - To maximise effect
    - To enhance bacterial eradication
    - To minimise development of R
- Strategies using PK/PD parameters

Real MIC = one necessary component !!

Improvement expected for clinical microbiology lab.

- Detection of resistance
- Determination of true MICs
- To be cost effective
  - To define clinical circumstances requiring MIC
  - To identify organisms requiring MIC
  - To define organisms, phenotypes or clinical circumstances requiring specific method for detection of R

Clinical circumstances worthy of MICs

- Patients
  - ICU or other high risk patients
- Infections
  - Endocarditis
  - Meningitidis
  - Cystic fibrosis, other chronic infections, sterile site infections
  - Serious nosocomial infections

Versus

SIR adequate for trivial uncomplicated infections

Treatment of streptococcal endocarditis

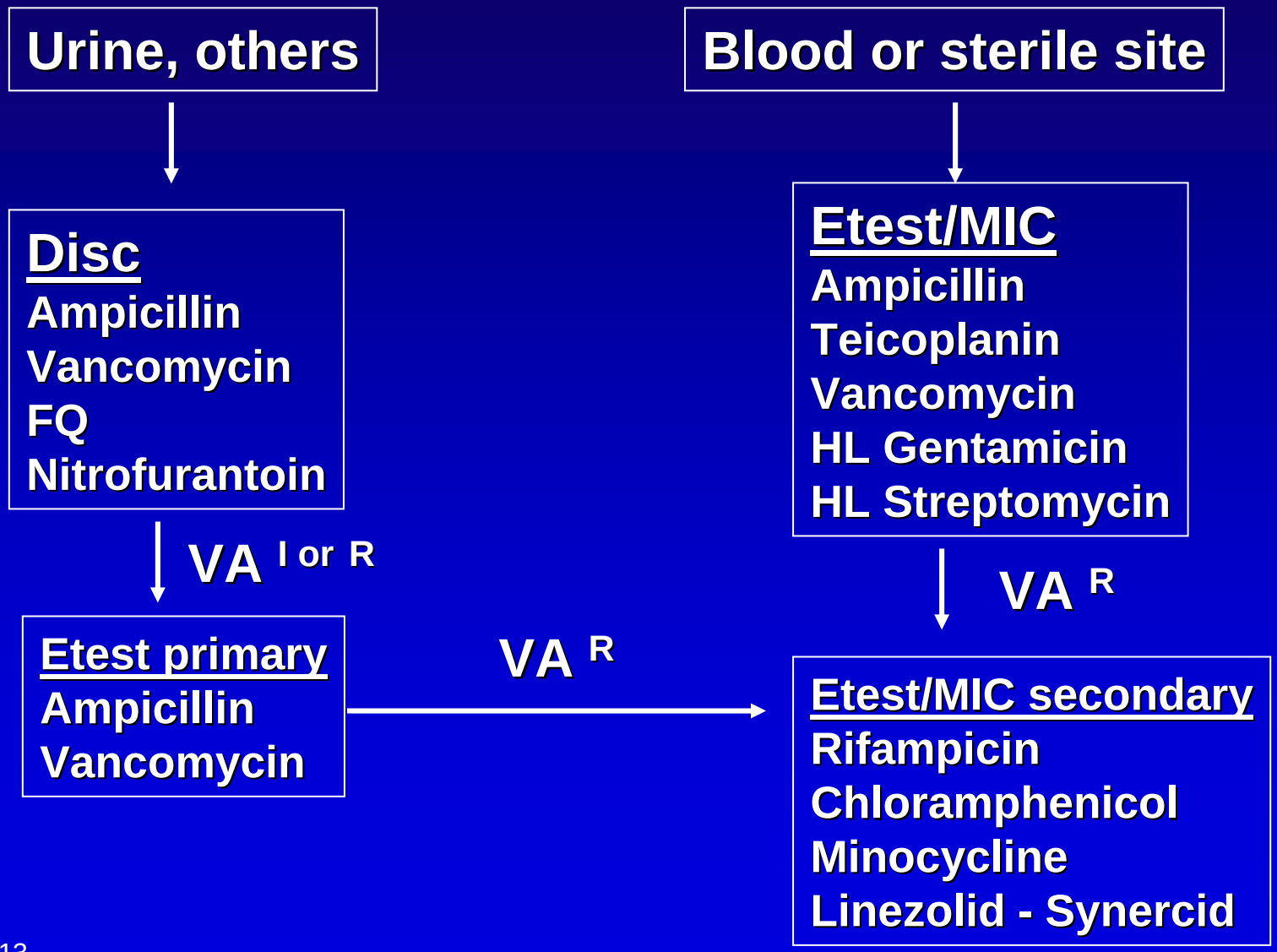
- MIC < 0.1 mg/L
  - Penicillin G for 4 weeks
- MIC 0.1-0.5 mg/L
  - Penicillin + gentamicin 2 weeks; penicillin 2 weeks
- MIC > 0.5 mg/L
  - Penicillin + gentamicin for 4-6 weeks

Organisms or type of R to detect worthy of Etest MICs

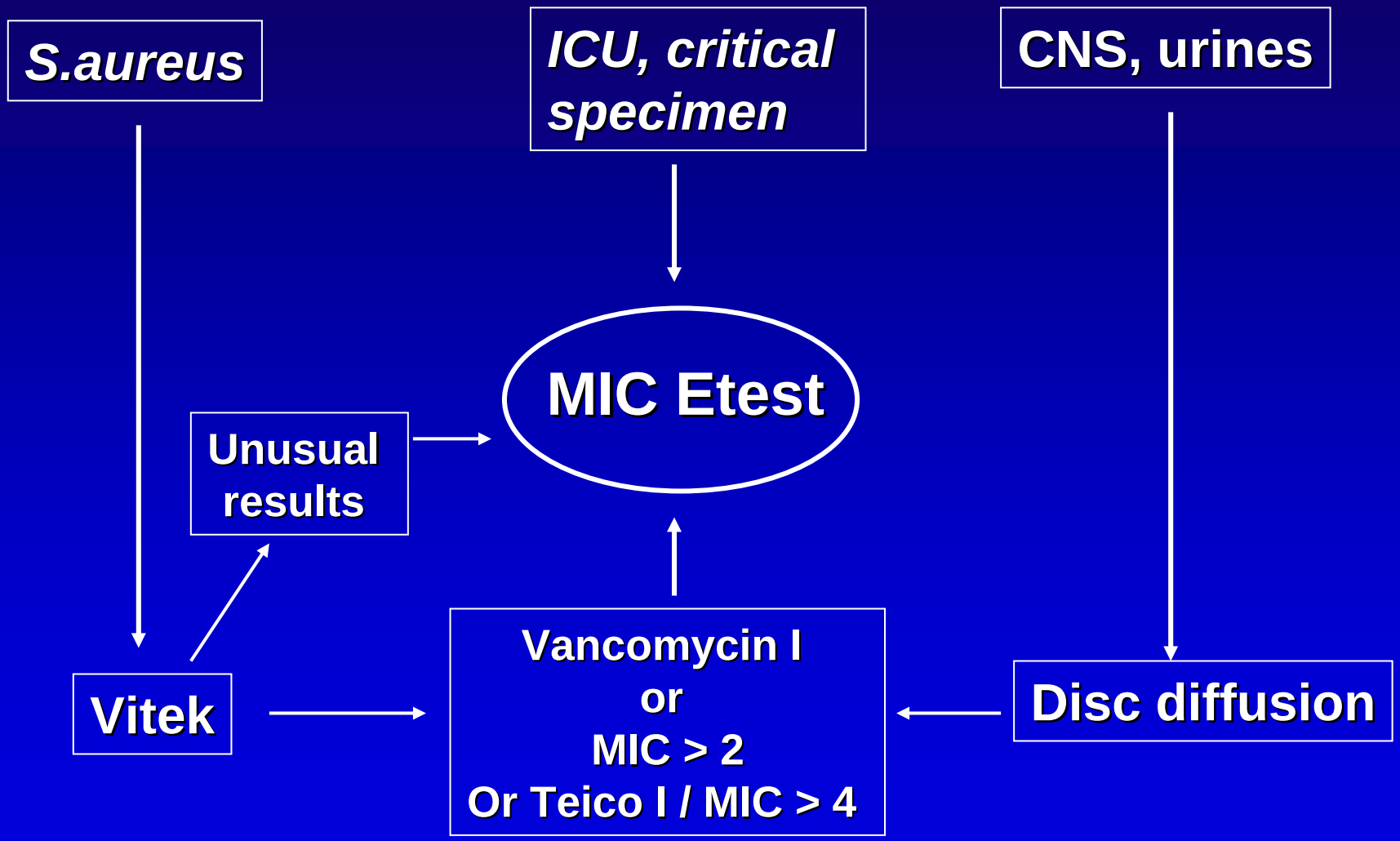
R proned, invasive, virulent

- *S.pneumoniae*
- *N.gonorrhoeae*
- Fastidious bacteria : NF GNB, GPB, etc
- Anaerobes
- Opportunist with no defined interpretative criteria
- Yeasts, fungi
- Confirmation / Detection of R
  - Penicilline (Pneumo)
  - Glycopeptides (staphylo, enterococci)
  - Oxacilline/SA
  - ESBLs, metallo-BLs

Enterococci AST algorithm



Staphylococci AST algorithm



Gram positive Bacilli AST algorithm

Sterile site, pure culture
Multiple positive blood cultures

Corynebacterium sp

Etest
Penicillin
Cefotaxime
Vancomycin
FQ

Bacillus sp

Etest
Penicillin
Clindamycin
Vancomycin
FQ