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KUCERS' THE USE OF ANTIBIOTICS

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KUCERS'

THE USE OF ANTIBIOTICS

A CLINICAL REVIEW OF ANTIBACTERIAL, ANTIFUNGAL, ANTIPARASITIC AND ANTIVIRAL DRUGS

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6TH EDITION

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Foreword to Kucers' "The Use of Antibiotics"

Robert C Moellering Jr

While one generally thinks of antibacterial agents as unique and important contributions to the battle against infectious diseases in the 20th Century, our modern antimicrobial agents are not the first effective drugs to be discovered and used to treat human infections. Quinine (as an extract from the bark of the cinchona tree initially found in the Andes) was discovered and utilized as an effective antimalarial agent by Europeans since the 17th Century (Snowden, 2006). It played a major role in the colonial expansion of the European powers thereafter and it, not Salvarsan, was really the first "magic bullet" of antimicrobial chemotherapy. Moreover, when one tracks back through history one finds that agents with antibacterial activity such as copper salts, honey grease, and myrrh were used for topical wound therapy (with no understanding of the basis for wound sepsis, of course) dating back to the time of the ancient Egyptians in 2500 BC and the Greeks and Romans thereafter (Majno, 1975). The ancient Chinese employed mouldy soybean curd which likely contained antimicrobial activity against wound pathogens as well (Majno, 1975). Nonetheless the bulk of the effort to discover antimicrobials and to learn the mechanisms by which they produce selective activity against microbes without harming their human hosts is a unique contribution of the 20th Century, beginning with Paul Ehrlich's discovery and clinical application of Salvarsan in the first decade of this century (Moellering, 1995). The flowering of research in antibacterials reached its zenith in the 1980's when many new agents were brought to clinical use and some "experts" including yours truly raised the possibility that the plethora of such agents might overwhelm the clinicians trying to discover their appropriate use (Murray and Moellering, 1981). However, these concerns have proven to be short lived and totally incorrect. Since then there has been a steady decline in the discovery and licensing of new antibacterial agents. The reasons for this are legion, but among them are the fact that most of the obvious bacterial targets for antimicrobials have been discovered and exploited; the fact that the cost of bringing new drugs to the market has skyrocketed; and the fact that there are increasing regulatory hurdles in certain countries including the United States (Talbot *et al.*, 2006). Add to this the fact that worldwide there is increasing resistance to antimicrobial agents among key bacterial pathogens and one has the basis for a looming crisis.

But all is far from bleak. The discovery and successful application of antiviral chemotherapy is a particularly bright spot. Fifty years ago it was thought that it would be virtually impossible to develop antiviral agents with selective toxicity because of the unique ability of viruses to invade and take over replication of molecular processes in mammalian cells. When the AIDS era began in the early 1980's, this diagnosis was a virtual death sentence. The remarkable basic virology which led to a literal deconstruction and reconstruction of the HIV virus allowed the discovery of numerous potential points of attack and provided the basis for the discovery of a panoply of new agents, many studied in well-designed publicly funded trials that have demonstrated their efficacy in HIV infections. Indeed, the present edition of this textbook details 27 chapters on new antiviral agents directed at HIV. The use of these drugs has now converted AIDS from a universally fatal disease to a chronic disease controlled for years by effective antiviral agents and allowing a normal or near normal lifespan for many of its victims. Similar if somewhat less dramatic progress is being made in the discovery and development of other antiviral agents as well as new antifungal and antiparasitic agents which are well documented in this textbook.

In an era when large textbooks are in danger of becoming dinosaurs, Kucers' "The Use of Antibiotics" stands out. It brings together in 258 chapters and two large volumes a compendium of information on antimicrobial agents which is unmatched. A book which began as a single-authored *tour de force* by Alvis Kucers has evolved into a multi-authored therapeutic encyclopedia. The addition of antiparasitic agents in this edition means that it now covers the whole of antimicrobial therapy. It maintains the clinical bent which made the original Kucers texts so valuable for the physician dealing with infections, and incorporates enough basic science to be useful to microbiologists and researchers in the field as well. I am unaware of any textbook which provides such comprehensive coverage of the field and doubt that this work will be surpassed in the foreseeable future, if ever! My congratulations to Lindsay Grayson, his co-editors, and all of the authors of chapters in this remarkable contribution to the field of antimicrobial therapy. It is a monumental achievement!

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Obituary

Dr. Alvis Kucers
4/10/1933–15/2/2007

Dr Alvis Kucers, one of Australia's leading infectious diseases physicians, whose seminal textbook on the use of antibiotics became the cornerstone of clinicians' libraries for more than 30 years, has died of disseminated melanoma. He was 73.

Born in Latvia, Kucers arrived in Melbourne from war-torn Europe in 1950, aged 16 and unable to speak English. When introduced by the headmaster to his new year 11 class at University High School, he was mistakenly announced to the other students as planning to do medicine (in fact, he meant to say "law", but got the English words muddled). Two years later he graduated with honours and a sporting award for soccer.

Despite the initial confusion in his career choices, he decided to study medicine after all and graduated second in his year from Melbourne University in 1957. He completed his residency at Royal Melbourne Hospital, then trained as a specialist physician while working at Fairfield Hospital. Soon after he was appointed as a junior clinician at Fairfield.

In 1968, the director, Dr John Forbes, encouraged Kucers to undertake a three-month hospital-funded trip to the US; both men believed the US approach of training infectious diseases physicians, rather than the European focus on training clinical microbiologists, was likely to become important.

Kucers was impressed with the US approach but recognised some confusion regarding how best to use the new antibiotics that were being rapidly developed at that time. When he returned from his study tour in 1969, he wrote an antibiotic booklet to assist trainee doctors in understanding how best to use these agents.

Forbes recognised the value of Kucers' clear, practical writing style for practising clinicians and encouraged him to publish the first edition of Use of Antibiotics in 1972.

Kucers regularly attended key international meetings, where he was highly respected for his authoritative comments on practical issues relating to the use of antibiotics. He was appointed to a number of World Health Organization committees to advise on antibiotic use in developing countries, and he helped develop the current "Essential Drug List" – a key guide for national health departments.

Kucers updated his Use of Antibiotics through five editions (the last in 1997) and made sure that all the contracts and details were signed off for the forthcoming sixth edition. In writing Use of Antibiotics, he was an incredible taskmaster for himself and others who worked with him. For those of us who had the great honor of co-writing the fifth edition with him, he was tremendously supportive and encouraging, while being totally dogged, self-disciplined and single-minded in his insistence on consistency of style, format and meeting chapter deadlines.

The worldwide recognition achieved by Use of Antibiotics is a total credit to Kucers.

In 1981, he took over as director of medical services at Fairfield Hospital following the mass resignation of senior medical staff due to administration problems. His appointment calmed the many political tensions and the following 10 years under his leadership became a key time for the hospital as it took on a leading national role in managing the emerging HIV-AIDS epidemic, assessing new anti-HIV drugs and caring for the many infected patients who were often suffering discrimination in other hospitals.

For Victorian public health, those were the glory years, with the then chief health officer, Dr Graham Rouch, and Kucers providing an impressive media tag-team; the public was calmly informed of the important facts, and the steps being put in place to manage the issue. Many Victorian health ministers slept soundly at night because of the skill, honesty and authority of these two men.

The early 1990s, however, were a more difficult period, with the concerted and ultimately successful government attempt to close Fairfield Hospital. To Kucers, Fairfield's closure highlighted the lack of understanding about the hospital's importance to infectious diseases training and the public health of Victorians. Generations of Melbourne and Monash university medical students benefited from the infectious diseases training they received from Kucers and other key staff at Fairfield.

Kucers was a tremendous mentor for trainee infectious diseases registrars, encouraging them to look beyond Australia's shores to widen their experience.

In recognition of his contribution to Australasian infectious diseases, in 2002 he was made a life member of the Australasian Society for Infectious Diseases.

He is survived by his longtime partner, Anne Smith, who nursed him tirelessly in his difficult last months, his brother, son and daughter.

The Age, Wednesday March 7, 2007
By Professor M. Lindsay Grayson, President, Australasian Society for Infectious Diseases

Preface

This 6th Edition starts with an inaccuracy since it no longer simply describes "the use of antibiotics", but instead aims to outline the clinical use of all antimicrobials-antibiotics, antifungals, antiparasitic and antiviral agents. As clinicians this seemed a logical next step from the previous editions where although there had been some evolution into antivirals and antifungals, the majority of the text was related to antibiotics. This expansion has mirrored the massive growth in knowledge and number of active agents for various infections since the last edition, but has come at the price of a hugely expanded text – increasing from 146 chapters in the 5th edition to 258 chapters; from 1950 pages to more than 3000 pages and from one volume into two. Where appropriate we have either deleted chapters on older, little-used agents, or more often amalgamated them into single chapters that provide an overview, and then directed the reader to previous editions for more information. The dilemma we faced in electing to expand the book was the sheer number of drugs and time needed to adequately research these. It was for this reason we decided to expand the authorship and establish eight section editors – but to maintain the system where all chapters were written under strictly defined sub-headings. New features include a diagram of the chemical structure for each compound, many more tables to better summarise susceptibility data, drug dosing and to collate important clinical trials, and new sections regarding clinically important pharmacokinetic/pharmacodynamic data and drug interactions.

Many have argued that textbooks are no longer necessary, given the growth of the internet and search capabilities via PubMed or Medline. However, it is our view that there is now simply so much information available, that reference texts such as this are important to help collate these data and to make sense of it all – we hope we have achieved this.

For those of us who had the good fortune and honour to train with Dr Alvis Kucers and to become his colleague and friend, we hope we have been able to live up to the high standards he always demanded– to focus on the important clinical issues that relate to patient care, to balance the important anecdote with the randomized double-blind trial and to describe the data in a way that is interesting and useful to health professionals who treat patients.

Of course, the 6th Edition would not be possible without the hard work and commitment of the international cast of distinguished authors, the eight section editors and the patience of staff at Hodder, including Sarah Penny, Caroline Makepeace and many others.

Alvis Kucers was a very special person – we hope he would be happy with the 6th Edition, which we have named in his honour.

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Abbreviations

5-FU	5-fluorouracil
AAC	aminoglycoside acetyltransferase
ACT	artemisinin-based combination therapies
AE	adverse event
AECB	acute exacerbations of chronic bronchitis
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AOM	acute otitis media
ART	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area-under-the-concentration-time curve
BAL	Bronchial alveolar lavage
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
BSAC	British Society for Antimicrobial Chemotherapy
CA-MRSA	Community-acquired MRSA
CAP	community-acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CAT	chloramphenicol acetyltransferase
CDAD	*Clostridium difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CFU	colony forming units
CHB	chronic hepatitis B
CHSS	chlorhexidine-silver sulfadiazine
CI	confidence interval
CL	clearance
CLSI	Clinical and Laboratory Standards Institute
CMS	colistin methanesulfonate
CNS	central nervous system
CPK	creatine phosphokinase
CRBSI	catheter-related bloodstream infection
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CSF	cerebrospinal fluid
cSSI	complicated skin and skin structure infections
CVVH	continuous venovenous hemofiltration
CVVHD	continuous venovenous hemodialysis
CYP	cytochrome P-450
ClCr	creatinine clearance
CoNS	coagulase-negative staphylococci
DEXA	dual-energy X-ray absorptiometry
DHBV	duck hepatitis B virus
DHFR	dihydrofolate reductase
DHHS	Department of Health and Human Services
DHPS	dihydropteroate synthetase
DRV	darunavir
EAP	Expanded Access Program
EBA	early bactericidal activity
EBV	Epstein-Barr virus
EC	effective concentration
ECG	electrocardiogram
EF	elongation factor
EFV	efavirenz
ELF	epithelial lining fluid
ESBL	extended-spectrum beta-lactamase
ESR	erythrocyte sedimentation rate
EUCAST	European Commitee on Antimicrobial Susceptibility Testing
F/M	Fetal/maternal
FDA	Food and Drug Administration
INR	international normalized ratio
FTC	emtrictiabine
G6PD	glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GFR	glomerular filtration rate
GI	gastrointestinal
GIQ	genotypic inhibitory quotient
GISA	Glycopeptide-intermediate resistant *Staphylococcus aureus*
GLUT1	glucose transporter type 1
GVHD	graft-versus-host-disease
HA-MRSA	hospital-acquired MRSA
HAP	hospital-acquired pneumonia
HBV	hepatitis B virus
HCAP	healthcare-associated pneumonia
HD	high-dose
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLAR	high-level aminoglycoside-resistant
HPLC-MS	high-pressure liquid chromatography and mass spectrometry
HPLC	high-performance liquid chromatography
IC	invasive candidiasis
ICU	Intensive Care Unit
INH	isoniazid
INR	International Normalized Ratio
IPC	inositol phosphoceramide
IPTi	intermittent preventive therapy of malaria in infants
IPTp	intermittent preventive therapy of malaria during pregnancy
ITT	intent-to-treat
IU	international unit
IgG	immunoglobulin G
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LPS	lipopolysaccharide
LPV	lopinavir

MAC	*Mycobacterium avium* complex
MAX	maximal concentration
MBC	minimal bactericidal concentrations
MDR	multidrug resistant
MEF	middle ear fluid
MICs	minimum inhibitory concentrations
MLC	minimum lethal concentration
MPC	mutant prevention concentration
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectrometry
MSSA	methicillin-susceptible *Staphylococcus aureus*
MSW	mutant selection window
NADPH	nicotinamide adenine dinucleotide phosphate
NAG	*N*-acetyl-glucosaminidase
NAT2	N-acetyltransferase 2
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OAI	osteoarticular infections
OI	opportunistic infection
OP-MRSA	other-phenotype MRSA
OR	odds ratio
OTC	over-the-counter
PA-SME	post-antibiotic sub-MIC effect
PABA	p-aminobenzoate
PAE	post-antibiotic effect
PBMC	peripheral blood mononuclear cells
PBP	penicillin-binding protein
PCR	polymerase chain reaction
PD	peritoneal dialysis
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PFGE	Pulsed-field gel electrophoresis
PFOR	pyruvate:ferredoxin oxidoreductase
PI	protease inhibitor
PID	pelvic inflammatory disease
PK-PD	pharmacokinetic-pharmacodynamic
PK	pharmacokinetic
PMN	human polymorphonuclear leukocyte
PNP	purine nucleoside phosphorylase
POR	pyruvate oxidoreductase
PPI	proton pump inhibitor
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PSI	pneumonia severity index
PSSP	penicillin-susceptible *S. pneumoniae*
PT	prothrombin time
PTA	probability of target attainment
PVL	Panton-Valentine leukocidin
PrEP	pre-exposure prophylaxis
QRDR	quinolone resistance-determining region
RD	recommended dose
RNA	ribonucleic acid
SAE	serious adverse event
SBA	Serum bactericidal activity
SBP	spontaneous bacterial peritonitis
SCC	staphylococcal cassette cartridge
SDD	selective decontamination of the digestive tract
SIV	simian immunodeficiency virus
SJS	Stevens-Johnson syndrome
SME	sub-MIC effect
SNPs	Single nucleotide polymorphisms
SSD	silver sulfadiazine
SSSI	skin and skin structure infections
TAMS	thymidine analog mutations
TB	tuberculosis
TBW	total bodyweight
TDF	tenofovir disoproxil fumarate
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis
THF	tetrahydrofolic
TNF	tumor necrosis factor
TOC	test of cure
TPV	tipranavir
TSH	thyroid stimulating hormone
TdP	*torsades de pointes*
ULN	upper limit of normal
UTI	urinary tract infection
UV	ultraviolet
VAP	ventilator-associated pneumonia
VISA	vancomycin-intermediate-resistant *Staphylococcus aureus*
VRE	vancomycin-resistant enterococci
VREF	vancomycin-resistant *E. faecium*
VRSA	vancomycin-resistant *Staphylococcus aureus*
VVC	vulvovaginal candidiasis
Vdss	volume of distribution at steady state
Vss	volume of distribution at steady state
WHO	World Health Organization
WHV	woodchuck hepatitis virus
cART	combined antiretroviral treatment
cSSSI	complicated skin and skin structure infections
cccDNA	covalently closed circular DNA
dGTP	dideoxyadenosine triphosphate
ddI	2′,3′-dideoxyinosine
fAUC/MIC	Ratio of the free area under the concentration-time curve (f) over the MIC
fAUC	free area under the concentration-time curve
hGISA	heterogenous glycopeptide-intermediate *Staphylococcus aureus*
hVISA	heterogeneous vancomycin-intermediate *Staphylococcus aureus*
i.m.	intramuscular
i.v.	intravenous
mITT	modified intention to treat
microITT	microbiological intent-to-treat
s.c.	subcutaneously
uSSSI	uncomplicated skin and skin structure infection