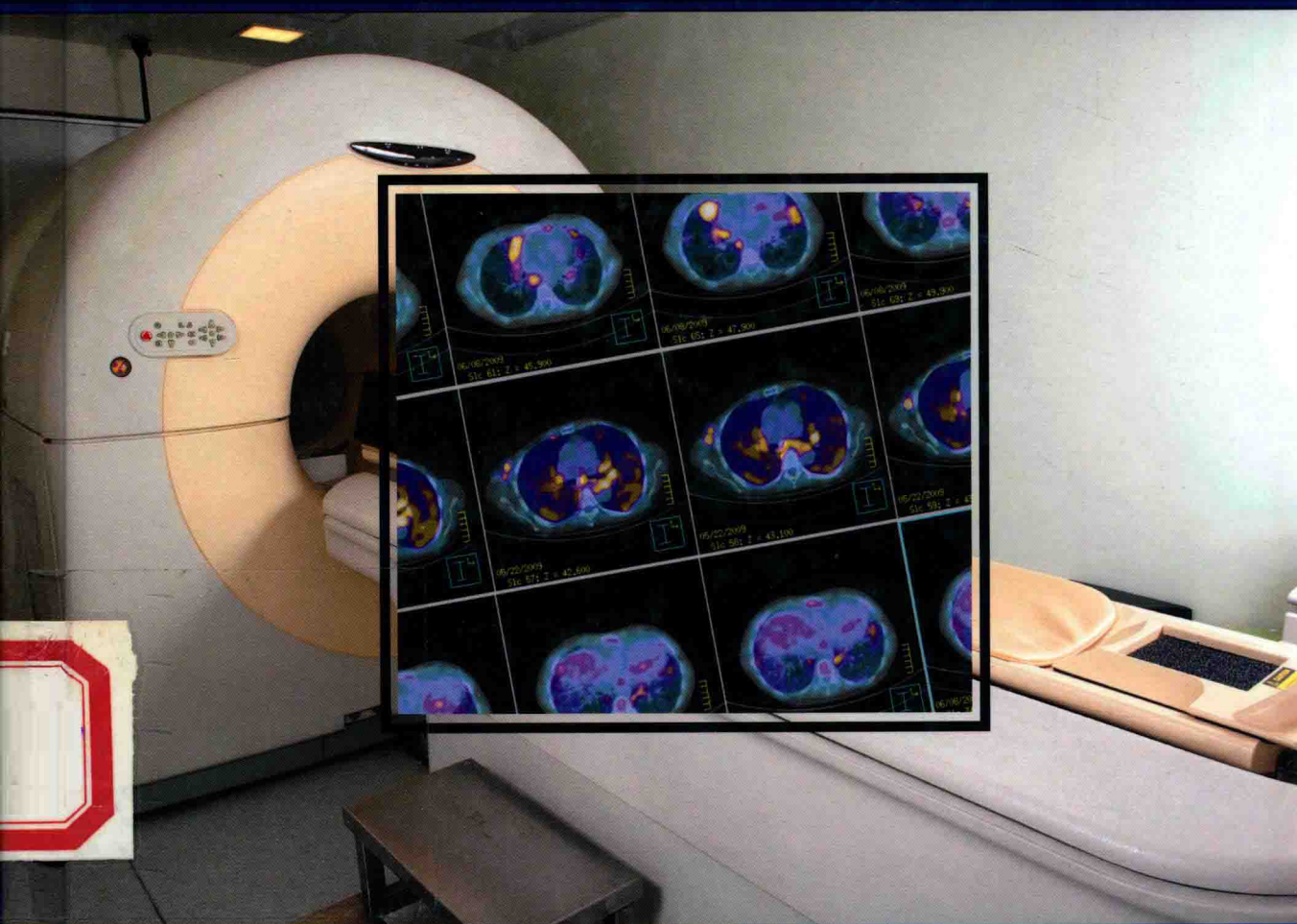


Diagnostic Imaging of Infections and Inflammatory Diseases

A Multidisciplinary Approach

Edited by **Alberto Signore** and **Ana María Quintero**



WILEY Blackwell

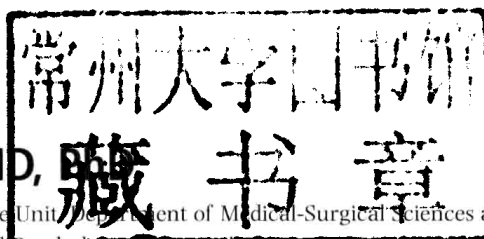
Diagnostic Imaging of Infections and Inflammatory Diseases

A Multidisciplinary Approach

EDITED BY

Alberto Signore, MD,

Professor of Nuclear Medicine, Nuclear Medicine Unit, Department of Medical-Surgical Sciences and of Translational Medicine, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy



Ana María Quintero, MD

Radiologist, Department of Radiology, Clínica Reina Sofía, Clínica Colsanitas, Bogotá, Colombia

WILEY Blackwell

Copyright © 2014 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey

Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permissions>.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by health science practitioners for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data

Diagnostic imaging of infections and inflammatory diseases : a multidisciplinary approach / edited by Alberto Signore, Ana Maria Quintero.

p. : cm.

Includes bibliographical references and index.

ISBN 978-1-118-48441-8 (alk. paper) – ISBN 978-1-118-48435-7 (print) –
ISBN 978-1-118-48438-8 (print) – ISBN 978-1-118-48439-5 (print) –
ISBN 978-1-118-48443-2 (print)

I. Signore, A. (Alberto), 1959- editor of compilation. II. Quintero, Ana Maria, editor of compilation.

[DNLM: 1. Diagnostic Imaging—methods. 2. Communicable Diseases—radiography.
3. Communicable Diseases—radionuclide imaging. 4. Inflammation—radiography.
5. Inflammation—radionuclide imaging. WN 180]
616.07'54—dc23

2013001677

Cover images: Main cover image © Baran Özdemir iStockphoto.com #17280971.

Inset image courtesy of Professor Signore.

Cover design by Matt Kuhns

Printed in Singapore

10 9 8 7 6 5 4 3 2 1

Diagnostic Imaging of Infections and Inflammatory Diseases

Francesca Maccioni, MD

Professor of Radiology, Department of Radiological Sciences, Faculty of Medicine and Dentistry, "Sapienza" University, Rome, Italy

Gaurav Malviya, PhD

Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands *and* Nuclear Medicine Unit, Department of Medical-Surgical Sciences and of Translational Medicine, Faculty of Medicine and Psychology, "Sapienza" University, Rome, Italy

Giuliano Mariani, MD

Professor of Nuclear Medicine, Regional Center of Nuclear Medicine, University of Pisa, Medical School, Pisa, Italy

Manuel Maynar, MD, PhD

Radiologist, Centro de Diagnóstico y Terapéutica Endoluminal CD y TE, Las Palmas de Gran Canaria University, Canary Islands, Spain

Christopher J. Palestro, MD

Professor of Radiology, Hofstra North Shore-LIJ School of Medicine, Hempstead, NY, USA *and* Chief, Division of Nuclear Medicine and Molecular Imaging, North Shore Long Island Jewish Health System, Manhasset & New Hyde Park, NY, USA

Nicola Petrosillo, MD

Director, 2nd Infectious Diseases Division, National Institute for Infectious Diseases, "L. Spallanzani", IRCCS, Rome, Italy

Ana María Quintero, MD

Radiologist, Department of Radiology, Clinica Reina Sofia, Clinica Colsanitas, Bogotá, Colombia

Sergi Quiroga, MD

Radiologist, Servicio de Radiodiagnóstico, Hospital Universitario Valle Hebrón, Barcelona, Spain

Zoraida Restrepo-Velez, MD

Research Fellow, NYU Medical Center, NYU Hospital for Joint Diseases, New York, NY, USA

Roy Riascos, MD

Associate Professor of Radiology, Department of Radiology, The University of Texas Medical Branch, Galveston, TX, USA

Alejandro Romero, MD

Radiologist, Servicio de Radiodiagnóstico, Hospital Universitario Valle Hebrón, Barcelona, Spain

Mike Sathekge, MBChB, MMed (Nucl Med), PhD, MASSAf

Professor & Head of Nuclear Medicine Department, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa

Giancarlo Schiappacasse, MD

Associate Professor of Radiology, Clínica Alemana, Facultad de Medicina, Universidad del Desarrollo, Santiago, Chile

Khalid Seghrouchni, MD

Department of Orthopedic Surgery, Geneva University Hospitals *and* Faculty of Medicine, University of Geneva, Geneva, Switzerland

Alberto Signore, MD, PhD

Professor of Nuclear Medicine, Nuclear Medicine Unit, Department of Medical-Surgical Sciences and of Translational Medicine, Faculty of Medicine and Psychology, "Sapienza" University, Rome, Italy

Martina Sollini, MD

Nuclear Medicine Physician, Regional Center of Nuclear Medicine, University of Pisa, Medical School, Pisa, Italy

Ilker Uçkay, MD

Department of Orthopedic Surgery, Department of Infectious Diseases, Geneva University Hospitals *and* Faculty of Medicine, University of Geneva, Geneva, Switzerland

Christophe Van de Wiele, MD, PhD

Professor and Head of Department of Nuclear Medicine, University Hospital Ghent, Ghent, Belgium

Carolina Whittle, MD

Professor of Radiology, Clínica Alemana, Facultad de Medicina, Universidad del Desarrollo, Santiago, Chile

Tobías Zander, MD, PhD

Radiologist, Centro de Diagnóstico y Terapéutica Endoluminal CD y TE, Las Palmas de Gran Canaria University, Canary Islands, Spain

Foreword

The care of patients presenting with signs of infectious or inflammatory diseases is often difficult because their symptoms are frequently non-specific; the diagnosis, differential diagnosis and decision about appropriate therapy is often a real challenge for the clinician. The implementation of the available diagnostic methods is complex and the evaluation of their results also complex and frequently contradictory. Many of these methods are not familiar to clinicians; therefore the decision about their role in the diagnostic process and the strategy to be adopted may be delayed. Most of the guidelines generally available still do not reflect consensual diagnostic strategies.

The editors of this book had the merit to involve clinicians, radiologists and nuclear physicians with the objective to review this difficult area disease by disease, to define the appropriate clinical questions that may arise in everyday practice and to compare the accuracy and diagnostic value of the available diagnostic methods. Their efforts have resulted in clear, didactic content that supports consultation in clinical practice, suggests solutions to the most frequently encountered pathological situations (osteomyelitis, spondylodiscitis, abdominal, soft tissue and vascular graft infections, HIV and chronic inflammatory diseases), and summarizes the consensual diagnostic strategies.

The book is an excellent illustration of the synergy that can be achieved between specialties and in the imaging specialties collaboration is of the utmost importance. Both radiology and nuclear medicine contribute, often in a complementary way, to obtaining the correct diagnosis and the timely evaluation of the therapeutic answer. The clear and objective comparison of the diagnostic value and performance of available methods in solving clinical problems allows us to define clear, precise, fast and less expensive diagnostic algorithms to assist clinicians for the benefit of our patients.

Representing our respective European professional-scientific communities (the European Association of Nuclear Medicine and the European Society of Radiology), we congratulate the editors and authors on their excellent work and recommend its exploitation by radiologists, nuclear physicians and clinicians.

Patrick Bourguet
Past President of the EANM
CRLCC Centre Eugène Marquis
Rennes, France

András Palkó
Past President of the ESR
University of Szeged
Szeged, Hungary

Preface

Having dedicated most of our scientific and clinical activity to the diagnosis of infections and inflammatory diseases we always had in mind to write a textbook on this topic. An initial book of this kind was published by one of us (AS) in early 2002, followed by a pictorial atlas and several chapters in other books dedicated to nuclear medicine and molecular imaging or to specific diseases. However, the multidisciplinary approach to diagnostic imaging of infections and inflammatory diseases has not been treated before in the systematic way that it is here.

We therefore combined our expertise and planned this multidisciplinary book by involving clinicians (infective disease specialists, endocrinologists, orthopedists and others), radiologists and nuclear medicine physicians. After initial enthusiasm we faced the difficulty of finding a common language among the contributors. Indeed, the way in which clinicians, radiologists and nuclear medicine physicians face and describe the same topic is very different, not only from a linguistic or medical point of view but, most importantly, in the way a patient is approached and images interpreted.

Clinicians tend to interpret images as “signs” and combine these with symptoms and other tests to reach the final diagnosis. Therefore, when describing images, they do it in the context of other tests, signs and symptoms, giving much less emphasis to the raw content of the image and all the possible functional–anatomical information that can be gained from images.

Radiologists usually prioritize a detailed anatomical description, some of which detail is irrelevant to the clinician, and aim to determine the diagnosis from identifying a multitude of anatomical features. When analyzing images, they carefully describe what they see and generally, will make a diagnosis only if anatomical abnormalities are found. But an anatomical abnormality is not always synonymous with disease and vice versa.

By contrast, in nuclear medicine, functional aspects and tissue characterization are more rele-

vant, thus providing different information from radiology, often complementary. Nuclear medicine examinations are closer to physiology and histopathology, while radiological examinations are closer to anatomy. Again, in nuclear medicine a physiological/histopathological abnormality is not always associated with a disease state. It is therefore important to define the threshold of normality for most examinations and the qualitative and quantitative analysis of images is not always helpful in this.

As a consequence, clinicians, radiologists and nuclear medicine physicians have different ways of describing diseases and different ways of writing medical textbooks.

It was important for us to attempt to give uniformity to the way in which the clinical problems are described in the different chapters. All chapters have the same structure and authors were “forced” to adhere to a common way of approaching the disease. This was not just an editorial exercise. In our view, it reflects the merging of the different disciplines in clinical practice and emphasizes the collaboration within multidisciplinary teams to reach the correct diagnosis for fast and efficient cure of the disease.

In the past 10 years in particular, nuclear medicine and radiology have merged considerably with the introduction of hybrid imaging (SPECT/CT, PET/CT and, more recently, PET/MRI). Therefore, for most patients the diagnostic imaging work-up is completed by the fusion of the two specialties and physicians are becoming more and more used to interpreting images using a common language. Therefore, this textbook is also a milestone in the formulation of common diagnostic flow charts for the diagnosis of infections and inflammatory diseases. It is addressed to medical students as well as specialists in nuclear medicine and radiology, and also to all clinicians involved in infectious/inflammatory diseases who require an up-to-date view of integrated diagnostic imaging in this field.

At the end of each chapter, we asked the authors to include three to five clinical cases to better

describe the diagnostic work-up of patients and to conclude these with the important teaching points that summarize the role of a particular imaging technique in a particular disease.

It has taken more than a year to thoroughly correct and edit, where necessary, all chapters in

order to make the textbook the result of a team effort rather than a multiauthor collection; a concept that makes this book unique and undoubtedly useful.

Alberto Signore
Ana María Quintero

Contents

List of Contributors, vii

Foreword, ix

Preface, x

Part I Infections and Host Response

- 1 Epidemiology of Infections in the New Century, 3
Nicola Petrosillo
- 2 Bacterial Osteomyelitis: The Clinician's Point of View, 15
Ilker Uçkay, Nicolas Christian Buchs, Khalid Seghrouchni, Mathieu Assal, Pierre Hoffmeyer and Daniel Lew

Part II Radiological Imaging

- 3 Radiological Imaging of Osteomyelitis, 29
Jenny T. Bencardino, Zoraida Restrepo-Velez, Randall Bujan and Diego Jaramillo
- 4 Radiological Imaging of Spine Infection, 54
Ana María Quintero and Roy Riascos
- 5 Radiological Imaging of Soft Tissue Infections, 75
Carolina Whittle and Giancarlo Schiappacasse
- 6 Radiological Imaging of Abdominal Infections and Inflammatory Disease, 91
Carolina Whittle, Giancarlo Schiappacasse and Francesca Maccioni
- 7 Radiological Imaging of Vascular Graft Infection, 118
Alejandro Romero, Tobias Zander, Jorge Lopera, Sergi Quiroga and Manuel Maynar
- 8 Radiological Imaging of Tuberculosis and Human Immunodeficiency Virus, 135
Jorge Carrillo

Part III Nuclear Medicine Imaging

- 9 Nuclear Medicine Imaging of Infections: Techniques, Acquisition Protocols and Interpretation Criteria, 149
Alberto Signore
- 10 Nuclear Medicine Imaging of Osteomyelitis: White Blood Cell, Monoclonal Antibody, or Bacterial Imaging?, 168
Christopher J. Palestro
- 11 Nuclear Medicine Imaging of Spondylodiscitis: The Emerging Role of PET, 187
Elena Lazzeri, Paola Anna Erba, Martina Sollini and Giuliano Mariani
- 12 Nuclear Medicine Imaging of Soft Tissue Infections, 199
Bárbara Morales Klinkert
- 13 Nuclear Medicine Imaging of Infections and Inflammatory Diseases of the Abdomen, 216
Josep Martín Comín, Alba Rodríguez Gasén and Christophe Van de Wiele
- 14 Nuclear Medicine Imaging of Vascular Graft Infection: The Added Role of Hybrid Imaging, 241
Ora Israel
- 15 Nuclear Medicine Imaging of Tuberculosis and Human Immunodeficiency Virus, 255
Mike Sathekge, Christophe Van de Wiele and Alberto Signore
- 16 Nuclear Medicine Imaging of Fever of Unknown Origin, 273
François-Xavier Hanin and François Jamar
- 17 Nuclear Medicine Imaging of Inflammatory Diseases, 291
Marco Chianelli, Gaurav Malviya, Andor W.J.M. Glaudemans and Alberto Signore

Index, 323

PART I

Infections and Host Response

CHAPTER 1

Epidemiology of Infections in the New Century

Nicola Petrosillo

National Institute for Infectious Diseases, "L. Spallanzani", IRCCS, Rome, Italy

Introduction

Over the past few decades, an alarming increase in infections caused by antibiotic-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* spp. (VRE), carbapenem-resistant *Pseudomonas aeruginosa*, extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* spp., carbapenemase-producing Enterobacteriaceae and multidrug-resistant (MDR) *Acinetobacter* spp., has been observed in the hospital setting and healthcare-associated facilities [1–4].

The main mechanisms of antimicrobial resistance result from convergence of multiple and different factors, depending on the pathogen: expression of low-affinity penicillin-binding proteins; the alternative pathway for peptidoglycan synthesis; low outer membrane permeability; and presence of genes encoding extended-spectrum, OXA-type (oxacillin-hydrolyzing) or metallo- β -lactamases, carbapenemases, intrinsic or acquired efflux pumps, and aminoglycoside and fluoroquinolone modifying enzymes.

These resistance determinants, depending on their origin, can be chromosomally encoded or acquired from mobile genetic elements, and easily transferred among microbial strains, thus conferring extended drug resistance upon them [5–7].

Numerous factors are associated with high rates of antimicrobial resistance in the healthcare setting, including pressure on antibiotic use, severity of illness, numerosity of invasive devices, length of hospital stay, immunosuppression, malnutrition and ease of cross-transmission of antimicrobial-resistant pathogens [8,9].

Staphylococcal infections: healthcare-acquired MRSA and beyond

In 2003, 59.5% of *S. aureus* isolates in the US National Nosocomial Infection Surveillance (NNIS) intensive care units (ICUs) were MRSA [10]. Similarly, in some European countries, according to European Antimicrobial Resistance Surveillance System (EARSS) data, greater than 60% of isolates in 2007, mostly in critical care areas, were MRSA [11]. However, during recent years, although MRSA rates in most European countries are high, a significant downward trend has been reported in many ICUs [12–14].

MRSA is one of the main pathogens in hospital settings, including surgery and intensive care, and is becoming an alarming problem also in nursing home and other healthcare facilities. Patients colonized with MRSA can easily develop an infection when they undergo invasive procedures. Indeed, the role of *S. aureus* nasopharyngeal carriage as a

risk factor for infection in the hospital setting has been widely documented [15]. Approximately 30% of colonized patients may develop an MRSA infection [16] and in nearly 20%, this is a bacteremia. In recent reports, carbapenem use has been related to MRSA colonization, with eight new cases of MRSA colonization per 1000 days of carbapenem therapy [17].

Despite the worldwide use of vancomycin, *S. aureus* resistance to this glycopeptide remains rare. Only nine cases of vancomycin-resistant *S. aureus* [VRSA; defined by a vancomycin minimum inhibitory concentration (MIC) of ≥ 1.6 mg/dL] have been identified to date and, as of 2007, approximately 100 vancomycin-intermediate *S. aureus* (VISA) isolates (defined by a vancomycin MIC of 0.4–0.8 mg/dL) have been reported worldwide [18].

Currently, the main concern is the shift in susceptibility to vancomycin, the so-called MIC “creep”. This phenomenon is represented by small incremental increases in vancomycin MIC within the susceptibility range. One of the most controversial issues in the treatment of MRSA is the evidence for reduced vancomycin treatment efficacy in the management of bacteremia and pneumonia by MICs at the upper limit of susceptibility (i.e. MICs of 0.2 mg/dL compared with ≤ 0.1 mg/dL, which are still considered to be susceptible) [19–25]. The increase in treatment failure might be the result of higher frequencies of hetero-resistance to vancomycin among isolates with vancomycin MICs of 0.2 mg/dL [26]. Indeed, VISA isolates are those with a MIC between 0.4 and 0.8 mg/dL, whereas heterogeneous VISA (hVISA) strains appear to be sensitive to vancomycin with a susceptibility range of 0.1–0.2 mg/dL, even though they contain a subpopulation of vancomycin-intermediate daughter cells (MIC ≥ 0.4 mg/dL) [27].

Finally, although MRSA infections were traditionally limited to hospitals, reports of community-associated cases of MRSA (CA-MRSA) infections began to emerge in the late 1990s in the USA [28]. CA-MRSA are genetically and phenotypically distinct from the typical multidrug-resistant healthcare-associated MRSA. These strains are resistant to β -lactam antibiotics and typically susceptible to other antistaphylococcal agents; they often encode for Panton–Valentine leukocidin (PVL) and other exotoxins and virulence factors [29].

The vast majority of CA-MRSA carry one of two smaller SCCmec types, IV and V, without the additional resistance genes. In general, they are more susceptible to non- β -lactam antibiotics and appear to be associated with increased transmission and hospitalization, skin and soft tissue infection and, rarely, severe diseases including necrotizing pneumonia [30].

CA-MRSA strains have rapidly emerged worldwide and are now endemic in the USA where they are amongst the most commonly isolated pathogens in emergency departments. Furthermore, nosocomial transmission of CA-MRSA and hospital outbreaks have recently been observed in several countries [31].

***Enterococcus* spp.**

Another emerging concern in surgery and intensive care areas is VRE diffusion [32]. Although the vast majority of clinical enterococcal infections are caused by *Enterococcus faecalis*, *Enterococcus faecium* has emerged in recent years as a major multiresistant nosocomial pathogen, with a great capacity for acquiring multiple antibiotic-resistance determinants, especially those encoding glycopeptide resistance (e.g. vanA- and vanB-resistance genotypes). Almost 100% of *E. faecium* isolates are now resistant to ampicillin, but high-level aminoglycoside resistance is also a major problem, as it is common in both *E. faecalis* and *E. faecium*, ranging from 25% to 50% in European countries.

Various risk factors for acquisition of VRE have been proposed, including environmental risk factors (extensive use of broad-spectrum antimicrobial agents; patient overcrowding in facilities; admission to an ICU, transplant ward or unit with high colonization pressure; contaminated surfaces and fomites where enterococci can survive for a long period even in dry conditions); patient risk factors (severity of illness; prolonged hospitalization; presence of indwelling catheters or invasive devices; prolonged mechanical ventilation; age; non-ambulatory status; immunosuppression as post-transplantation status; diarrhea; renal failure/chronic hemodialysis; and proximity to patients who are colonized by VRE); clinical risk factors (poor adherence to infection-control practices; unrecognized antimicrobial resistance in the facility; inappropriate treatment; and use of contaminated equipment) [33].

Multidrug-resistant Enterobacteriaceae: are we facing a new era?

Among Gram-negative agents, ESBL-producing Enterobacteriaceae are a great concern. The epidemiology of ESBLs has changed dramatically: until recently, most infections caused by ESBL-producing bacteria were described as being acquired nosocomially, often appearing in specialized units, but are now increasingly found in non-hospitalized patients, and the mode of transmission or source of this pathogen is still unknown [34,35].

More recently, the worldwide epidemic of Enterobacteriaceae resistant to carbapenems is also a major concern. Carbapenems have been widely used as the treatment of choice for serious infections caused by ESBL producers, exerting selection pressure for carbapenem resistance. *Klebsiella pneumoniae* carbapenemases (KPC)-type enzymes are emerging resistance determinants, especially for *K. pneumoniae* [36–38]. During the last decade, a rapidly evolving spread of KPC and β -lactamases has been documented worldwide, creating an endemic situation in many countries. KPC-associated infections are predominantly nosocomial and systemic infections, affecting patients with multiple risk factors [38,39]. Therapeutic failures and adverse impact on patient outcome, with high mortality rates ranging from 22% to 57%, have been reported [36].

Non-fermentative Gram-negative infections: a threat for critical patients

Multidrug-resistant non-fermentative organisms are a major concern in healthcare facilities worldwide. In more than 300 US hospitals surveyed by the Centers for Disease Control (CDC), rates of carbapenem resistance in *Acinetobacter baumannii* isolates increased from 9% in 1995 to 40% in 2004 [40]. *A. baumannii* infections, mainly ventilator-associated pneumonia (VAP) and bloodstream infections, frequently affect critically ill patients in ICUs with major risk factors, including older age, presence of severe underlying diseases, immunosuppression, major trauma or burn injuries, a scheduled invasive procedure, as well as the presence of indwelling catheters, invasive mechanical ventilation, extended hospital stay and previous administration of antibiotics [41,42].

Carbapenem resistance to *P. aeruginosa* ranges between 10% and 48% in ICUs worldwide [43] and

currently represents a major concern due to the lack of new drugs effective against these strains.

Prosthetic joint infections

The numbers of primary total hip and total knee arthroplasties has dramatically increased worldwide over the past decade. In 2006, about 800 000 hip and knee arthroplasties were performed in the USA [44] and 130 000 in England [45]. Kurtz *et al.* formulated projections for the number of primary and revision total hip and knee arthroplasties that will be performed in the USA through 2030 and estimated a 174% increase (572 000) in hip procedures per year and a 673% increase (3.48 million) in knee prosthesis per year [46]. While such procedures achieve great improvement in quality of life, the risk of infection represents a serious complication, occurring in 0.8–1.9% of knee arthroplasties and 0.3–1.7% of hip arthroplasties [47–49].

The incidence of joint prosthesis infection ranges between 1.5% and 2.5% for primary interventions and up to 20% for revision procedures; mortality ranges between 1% and nearly 3% [50]. The economic cost of this complication is up to \$50 000 per patient and \$250 000 million per year [51,52]. The increases in life expectancy and predicted number of joint replacement procedures are likely to register a significant increment in the number of prosthetic joint infections with a strong impact on countries' health economic balance in the next few years [53].

From an epidemiological point of view, joint prosthesis infections are classified in relation to the time of onset after surgery as "early" (first 3 months after surgery), "delayed" (between 3 months and 2 years after surgery) or "late" (>2 years after surgery). Table 1.1 shows the main risk factors for infection.

Microorganisms may reach the prosthesis at the time of implantation or later by hematogenous spread. The development of a biofilm has a strategic role in the pathogenesis of prosthetic joint infections. Foreign bodies remain devoid of a microcirculation that is crucial for host defense and the delivery of antibiotics. The biofilm represents a basic survival mechanism by which microbes resist external and internal environmental factors, such as antimicrobial agents and the host immune system [54].

Table 1.1 Risk factors for prosthetic joint infections

Patient-related risk factors
• Previous revision arthroplasty
• Previous infection associated with a prosthetic joint at the same site
• Tobacco abuse
• Obesity
• Rheumatoid arthritis
• Diabetes mellitus
• Neoplasm
• Immunosuppression
Surgical risk factors
• Simultaneous bilateral arthroplasty
• Long operative time (>2.5 hours)
• Allogeneic blood transfusion
Postoperative risk factors
• Wound healing complications
• Atrial fibrillation
• Myocardial infarction
• Urinary tract infection
• Prolonged hospital stay
• <i>S. aureus</i> bacteremia

Modified from Cataldo *et al.* [53] and Del Pozo and Patel [54].

The most frequent etiological agents are staphylococci, accounting for more than 50% of prosthetic joint infections. *S. aureus* is usually isolated in early infections, whereas coagulase-negative staphylococci are isolated in late infections, as well as streptococci (9–10%), enterococci (3–7%) and anaerobes (2–4%) [55,56].

Gram-negative bacteria, mostly *P. aeruginosa*, *Enterobacter* spp., *Proteus* spp. and other relatively uncommon agents have an important clinical impact because they are difficult to treat [57,58]. Overall, about 20% of prosthetic joint infections are polymicrobial and 7–11% are culture negative [59,60]. Unusual pathogens, such as *Candida* spp., *Brucella* spp. and mycobacteria have also been reported [61].

In the last decade there has been an increase in reports of infections due to antibiotic-resistant bacteria; in a large surveillance study on surgical site infection after orthopedic interventions, 59% of the *S. aureus* isolates were methicillin resistant, with a higher risk of treatment failure than for infections caused by methicillin-susceptible *S. aureus* [62].

Table 1.2 Rate of infection for prosthetic cardiovascular devices

Type	% Infection	
	First implant	Revision
Prosthetic heart valve	1–6	15
Pacemaker	1–2	3–30
Defibrillator	4	
Left ventricular assist device	50	
Vascular graft prosthesis	1–6	22
Hemodialysis tunneled catheter	12	
Hemodialysis arteriovenous graft	1–6	

Modified from Sampedro and Patel [64].

In conclusion, prosthetic joint infection represents a challenge for orthopedic surgeons, infectious diseases specialists, clinical microbiologists and all the other professionals involved in the care of patients receiving prosthetic joints. It is expected that the incidence of prosthetic joint infections will further increase due to better detection methods for microbial biofilms involved in prosthetic joint infections, the growing number of implanted prostheses in the aging population and the increasing residency time of prostheses, which are at continuous risk for infection during their implanted lifetime [63,64].

Prosthetic vascular infections

The medical device market in developed countries is exponentially growing [65] and represents a great health benefit and progress. However, infection is a challenging and growing problem associated with medical devices. In the USA, approximately 1 million nosocomial infections per year are related to indwelling medical devices [66]. In spite of the progress made in the prevention and treatment of device-associated infection, an increase in the number of patients with device-associated infections can be predicted from the increasing numbers of devices and the lifelong risk for bacterial seeding of devices (Table 1.2).

Prosthetic cardiovascular devices include heart valves, pacemakers, defibrillators, coronary artery

stents, artificial arteries, aortic stents, central venous catheters and arterial catheters. The frequency of long-term prosthetic device infection varies with the type of implant and rates of infection are greater after revision, likely due to several factors, including longer operation times of surgery and poor circulation as a result of scars around the previous implant. Rates of infection in first implants and in revision surgery, respectively, are 1–6% and 15% for mechanical and prosthetic heart valves [67,68]; 1–2% and 3–10% for pacemakers [69]; and 1–6% and 22% for vascular graft prostheses [70,71]. Additionally, rates of infection for defibrillators [72], left ventricular assist devices [73], hemodialysis tunneled catheters [74] and hemodialysis arteriovenous grafts [75] are 4%, 50%, 12% and 1–6%, respectively. Along with the increasing number of implanted devices, the number of cardiac device-related infections has increased 124% between 1990 and 1999, and the rate of prosthetic valve infection has increased 50% over the same period (from 0.26 to 0.38 cases per 1000 Medicare beneficiaries) [76,77].

The microbiology of these infections is related to the ability of organisms to constitute the extracellular matrix of the biofilm. In the biofilm state, microorganisms are relatively immune to antibodies and phagocytes [78] and are also more resistant than free-living organisms to conventional antimicrobial agents [79].

Staphylococcus spp. are the most common microorganisms associated with device-related infections. Adherence of *S. aureus* to devices is dependent on the presence of microbial surface components recognizing adhesive matrix molecules [80]. However, biofilm formation is not limited to staphylococci; other Gram-positive organisms, including streptococci, *Enterococcus* spp., *Propionibacterium acnes*, *Corynebacterium* spp. Gram-negative organisms, including *P. aeruginosa* and Enterobacteriaceae; and fungi can produce biofilm.

In the pathogenesis of prosthetic vascular infections the host also plays an important role: the inflammatory response secondary to surgery and subsequent platelet aggregation and release of adhesins gives potential for microbial colonization [81].

All types of prosthetic vascular grafts are susceptible to infection via direct contamination during implantation or bacteremia after operation. Despite

the use of perioperative systemic antibiotic prophylaxis, vascular graft infections still occur. To address this problem, antibiotic- and antimicrobial-impregnated grafts have been developed and their effectiveness assessed in experimental and clinical studies [82,83].

The gold standard for treatment of an infected prosthetic graft/device remains explantation and, for vascular grafts, subsequent reperfusion by placing a new graft, most commonly via an extra-anatomic uninfected route and less commonly via *in-situ* grafting using an autogenous (vein) conduit. Antimicrobial therapy is a vital adjunct to surgical management; in some cases it may be the only option if the patient is not fit for further operative intervention.

As the number of prosthetic vascular device increases, the development of new solutions for prevention and management of infections represents the challenge for the next decades.

Skin and soft tissue infections

Skin and soft tissue infections (SSTIs) reflect inflammatory microbial invasion of the epidermis, dermis and subcutaneous tissues, and can be considered to be the commonest infection in humans. SSTIs can be classified according to anatomical site, microbiological etiology, or severity. In 2003, an expert panel classified SSTIs according to the severity of local and systemic signs, thereby developing a system that guides the clinical management and treatment decisions for patients with SSTIs [84]. In 2005, the practice guidelines of the Infectious Diseases Society of America (IDSA) for the diagnosis and management of skin and soft tissue infections classified SSTIs into five categories: superficial, uncomplicated infection (includes impetigo, erysipelas and cellulitis); necrotizing infection; infections associated with bites and animal contact; surgical site infections; and infections in the immunocompromised host [85]. The Surgical Infection Society (SIS) has recently published new guidelines for the treatment of complicated SSTIs [86]. The guidelines deal exclusively with complicated SSTIs, including those that are deep or necrotizing, usually requiring surgical intervention (infected ulcers, infected burns and major abscesses) and occurring in patients with specific major co-morbidities that necessitate hospitalization.

The epidemiology of complicated SSTIs has changed somewhat in the last decade. The frequency of SSTIs has increased significantly since the late 1990s, predominately because of an increase in infections caused by CA-MRSA [87].

What has changed in *S. aureus* infections? Since its first appearance in 1961, in the past two decades the prevalence of MRSA has become widespread in hospitals, particularly in ICUs, representing a substantial burden in terms of morbidity, mortality and cost. It was estimated that deaths in patients with MRSA in the USA in 2005 surpassed those caused by human immunodeficiency virus (HIV) in the same year [88,89]. The increase in MRSA infections most likely reflects the growing impact of medical interventions, devices, older age and co-morbidities of patients. All of these represent risk factors for healthcare-associated (HA) MRSA infection, along with antibiotic use and overuse [90]. While the frequency of MRSA infections continues to grow in hospital settings [91], of rising concern is the emergence of MRSA in patients without apparent risk factors presenting from the community. Since 1998, several outbreaks of community-associated (CA)-MRSA in children, athletes, prisoners, military personnel, men who have sex with men, HIV-infected people, native Americans and aboriginal populations have been reported [89]. The prevalence of CA-MRSA infections varies widely according to region, reaching 20–50% of SSTIs in US cities [92]. Although initially thought to have spread from hospitals to the community, several studies have revealed a number of genetic and epidemiological differences between HA-MRSA and CA-MRSA [92]. CA-MRSA genetic features include the staphylococcal cassette chromosome *mec* (SCC*mec*) IV and V elements as the mechanism of methicillin resistance, and the gene encoding for the Panton–Valentine leukocidin (PVL) toxin.

Regarding the main pathogens isolated from SSTIs, data from the SENTRY Program, which includes 5800 consecutive patients admitted to hospitals in Canada and 32 states in the USA, show that *S. aureus* remains the most common pathogen isolated from complicated SSTIs, accounting for greater than 40% of all isolates, with *P. aeruginosa* being the second most common isolate (11%). Between 1998 and 2004, the number of SSTI pathogens resistant to at least one antibiotic increased for *S. aureus*, *Enterococcus* spp., *P. aeruginosa*, *E. coli*

and *Klebsiella* spp., with nearly 50% of the *S. aureus* isolates being resistant to methicillin [93]. Regarding surgical site infections (SSIs), which occur in more than 5% of patients undergoing surgery [94], the epidemiology is slightly different, with an even greater shift toward Gram-positive pathogens (*S. aureus*, coagulase-negative staphylococci and *Enterococcus* spp. in >50% of isolates) [95].

Management of complicated SSTIs is particularly challenging, because prompt recognition, timely surgical debridement or drainage, resuscitation if required and appropriate antibiotic therapy represent the cornerstones of clinical success. The mainstays of antimicrobial treatment are the penicillins, cephalosporins, clindamycin and co-trimoxazole. β -Lactam/ β -lactamase inhibitor combinations are indicated for polymicrobial infection. A range of new agents for the treatment of MRSA infections has been compared with the glycopeptides; some of them, including daptomycin, linezolid and tygecilcline, have distinct pharmacokinetic advantages.

Tuberculosis and human immunodeficiency virus in the new century

An ancient pathogen, *Mycobacterium tuberculosis*, and a new one, HIV, met about 30 years ago; their interaction resulted in an escalation of the burden of both diseases and also of their morbidity and mortality. This was more evident in those countries where HIV and tuberculosis (TB) were highly prevalent, and health and social conditions the poorest.

The history of dual TB/HIV infection has faced increasing challenges in the last decades, beginning with an exponential rise in TB case notifications in sub-Saharan Africa, a high case fatality rate [96], high rates of TB recurrence [97] and increased transmission in settings where people congregate. In industrialized countries, outbreaks of multidrug-resistant (MDR) TB have occurred since the 1990s in HIV-infected patients in healthcare facilities [98]. In 2005–2006 there was the dramatic outbreak of extensively drug-resistant (XDR) TB in HIV-infected individuals in a rural area in South Africa [99].

In the pre-HIV era, there was a marked improvement in TB management thanks to the expansion of directly observed therapy, short-course (DOTS) programs. When cases of HIV-associated TB dramatically rose, there was the clear demonstration