PART I

Infections and Host Response
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 Actinobacter 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].
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

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**Table 1.1** Risk factors for prosthetic joint infections

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
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<tr>
<td>• Previous revision arthroplasty</td>
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<tr>
<td>• Previous infection associated with a prosthetic joint at the same site</td>
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<tr>
<td>• Tobacco abuse</td>
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<td>• Obesity</td>
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<td>• Rheumatoid arthritis</td>
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<td>• Diabetes mellitus</td>
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<td>• Neoplasm</td>
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<td>• Immunosuppression</td>
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<tr>
<th>Surgical risk factors</th>
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<tr>
<td>• Simultaneous bilateral arthroplasty</td>
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<td>• Long operative time (&gt;2.5 hours)</td>
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<tr>
<td>• Allogeneic blood transfusion</td>
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<tr>
<th>Postoperative risk factors</th>
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<tr>
<td>• Wound healing complications</td>
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<tr>
<td>• Atrial fibrillation</td>
<td></td>
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<tr>
<td>• Myocardial infarction</td>
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<tr>
<td>• Urinary tract infection</td>
<td></td>
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<tr>
<td>• Prolonged hospital stay</td>
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<tr>
<td>• <em>S. aureus</em> bacteremia</td>
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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>
<thead>
<tr>
<th>Type</th>
<th>% Infection</th>
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<tbody>
<tr>
<td><strong>First implant</strong></td>
<td><strong>Revision</strong></td>
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<tr>
<td>Prosthetic heart valve</td>
<td>1–6</td>
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<tr>
<td>Pacemaker</td>
<td>1–2</td>
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<tr>
<td>Defibrillator</td>
<td>4</td>
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<tr>
<td>Left ventricular assist device</td>
<td>50</td>
</tr>
<tr>
<td>Vascular graft prosthesis</td>
<td>1–6</td>
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<tr>
<td>Hemodialysis tunneled catheter</td>
<td>12</td>
</tr>
<tr>
<td>Hemodialysis arteriovenous graft</td>
<td>1–6</td>
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</table>

Modified from Sampedro and Patel [64].

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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 (SCCmec) 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 tygeclline, 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...
that DOTS alone could not contain the epidemic [100]. Immediately in many African countries TB became the leading cause of death in adults with HIV infection [101] and TB was recognized worldwide as one of the commonest causes of morbidity in the course of HIV infection.

HIV is the strongest risk factor for developing TB disease in those with existing or newly acquired M. tuberculosis infection. The risk of developing TB is between 20 and 37 times greater in people living with HIV than amongst those who do not have HIV infection. In 2009, of an estimated 14 million TB cases globally, 1.6 million were HIV positive [102]. TB is responsible for more than a quarter of deaths in people living with HIV. In 2007, 456,000 deaths occurred in HIV-infected people with TB, representing 23% of the estimated 2 million deaths from HIV infection for that year [103]. These estimated numbers of HIV-related TB cases and deaths were nearly double those reported in previous years, although this is indicative of improved data collection rather than a real change in epidemiology.

The resistance of M. tuberculosis to specific drugs represents another challenge. MDR-TB emerged as a clinical entity in the early 1990s after a couple of decades of widespread use of rifampin. TB rates increased five-fold in sub-Saharan Africa during the 1990s because of HIV infection, and the lack of careful systems of treatment and prophylaxis led to the emergence of MDR-TB, the rate of which aggressively and exponentially increased in the Russian Federation and, later, in areas of sub-Saharan Africa with the highest burden of HIV infection [104,105]. The World Health Organization (WHO) detected an increase in the global caseload of MDR-TB from about 274,000 cases in 2000 to about 500,000 cases in 2007 (5% of the global case burden of TB) [102,106,107]. Most funding and resources for TB control are diverted to MDR-TB, since MDR-TB outcome is poorer than that of drug-sensitive TB [108].

Moreover, another threat has recently appeared with the emergence of XDR-TB, i.e. TB with resistance, at least, to rifampin and isoniazid, plus any fluoroquinolone and any of the injectable agents (amikacin, kanamycin or capreomycin). XDR-TB is more expensive to treat than MDR-TB and outcomes are poorer, particularly in patients who are HIV positive [109].

The dual HIV/TB epidemic represents a challenge for industrialized and developing countries and is a major problem for people living with HIV in resource-constrained settings. Therefore, the WHO has recommended 12 collaborative TB/HIV activities as part of core HIV and TB prevention, care and treatment services. They include interventions that reduce the morbidity and mortality from TB in people living with HIV, such as the provision of antiretroviral therapy and the “Three Is” for HIV/TB: intensified case finding of TB, isoniazid preventive therapy and infection control for TB [103, 110, 111] (Table 1.3).

Finally, providing good HIV care for HIV-infected people who develop TB represents a fundamental element in the management of TB/HIV patients. Provider-initiated HIV testing and counseling, co-trimoxazole preventive therapy and antiretrovirals should be regarded as the basic standard of care and yet gaps in implementation remain large. About 40% of all patients with TB are not tested for HIV and a large proportion with HIV infection and TB lack access to co-trimoxazole preventive therapy and antiretroviral therapy [102,112,113].

Table 1.3 WHO recommended collaborative activities against the dual epidemic of TB/HIV

<table>
<thead>
<tr>
<th>1. Establish the mechanisms for collaboration:</th>
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<tbody>
<tr>
<td>• Set up a coordinating body for TB/HIV activities that is effective at all levels of the health system</td>
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<tr>
<td>• Conduct surveillance of HIV prevalence among TB patients</td>
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<tr>
<td>• Carry out joint TB/HIV planning for resources, capacity building, communication, community participation and operational research</td>
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<td>• Conduct monitoring and evaluation</td>
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<tr>
<td>2. Decrease the burden of tuberculosis in people living with HIV/AIDS</td>
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<tr>
<td>• Establish intensified tuberculosis case finding</td>
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<tr>
<td>• Introduce isoniazid preventive therapy</td>
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<tr>
<td>• Ensure TB infection control in the healthcare setting and in congregation settings</td>
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<tr>
<td>3. Decrease the burden of HIV in patients with TB</td>
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<tr>
<td>• Provide HIV testing and counseling</td>
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<tr>
<td>• Introduce methods to prevent HIV</td>
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<tr>
<td>• Introduce co-trimoxazole prophylaxis</td>
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<tr>
<td>• Ensure HIV/AIDS care and support</td>
</tr>
<tr>
<td>• Introduce and provide antiretroviral treatment for HIV/TB individuals</td>
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</tbody>
</table>

Modified from Harries et al. [103] and WHO [111].
As the HIV-associated TB epidemic is continuing, bold but responsible action is needed in terms of better service provision, infection control and sound initiatives to minimize the impact of this dual infection in the new century.

References


Harcombe AA, Newell SA, Ludman PF et al. Late complications following permanent pacemaker implantation or elective unit replacement. Heart 1998;80:240–244.


