Emerging Infectious Diseases of the 21st Century

I. W. Fong

Current Trends and Concerns in Infectious Diseases

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I. W. Fong
St. Michael's Hospital
University of Toronto
Toronto, ON, Canada

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This book is dedicated to my grandchildren:
Miranda and Aiden.

Preface

Current Trends and Concerns in Infectious Diseases is a sequel to the successful book *Emerging Issues and Controversies in Infectious Diseases* published in 2009, which was well received by the academic medical community. This is a new volume of the series "Emerging Infectious Diseases of the 21st Century." This volume deals with important developing trends in various aspects of infectious diseases that are relevant to practicing and academic physicians, investigators, and trainees (residents or fellows) in infectious diseases, infection control, public health, and global health. The first two chapters deal with issues and trends in human immunodeficiency virus (HIV) infection such as prevention with preexposure prophylaxis (PReP) and postexposure prophylaxis (PEP), universal access to antiretroviral therapy (ART), and development of an effective HIV vaccine. The second chapter addresses the issue of complication of management: the immune reconstitution syndrome (IRS)—the pathogenesis, diagnosis, manifestation, and management.

The next four chapters deal with trends and issues in the management of community-acquired pneumonia, *Helicobacter pylori* infection, hepatitis B and C infections, and the increasing occurrence of infectious complications of new and emerging biological agents. Other topics with controversial issues dealt with later in the book include chapters "Issues in the therapeutics of some bacterial infections: Vancomycin use, osteomyelitis, endocarditis, and *Staphylococcus aureus* bacteremia," "Issues and concerns in the management of systemic candidiasis," and "Emerging and difficult to treat nontuberculous mycobacterial infections." The chapters review the epidemiology, pathogenic mechanisms, diagnosis, therapeutics, and prevention, plus viewpoints on controversial issues.

Three chapters address issues of global health and concerns in communities that may affect and be relevant to many millions of the world's population: "Climate change: Impact on health and infectious disease globally," "Blood transfusion-associated infections in the twenty-first century: New challenges," and "Mass drug treatment of tropical diseases: Is it really progress?."

Toronto, ON, Canada — I. W. Fong

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About the Authors

I. W. Fong is the Editor of Springer's *Emerging Infectious Diseases of the 21st Century* series. He has served as Chief Editor for six books and is the sole author for another six books published in the series. He completed his residency training in Internal Medicine at the University of Toronto and as a Fellow in Infectious Diseases at the University of Washington, Seattle. Dr. Fong has published studies concerning a variety of infectious diseases that include therapeutics and pharmacology of antibiotics, AIDS and the treatment of opportunistic infections, mechanistic and treatment studies of mucosal candidiasis, and pathogenic studies on infection and induction of atherosclerosis in animal models. He was Chief of Infectious Diseases at St. Michael's Hospital (Toronto) for 34 years; he is still on staff in Infectious Diseases and is a Professor of Medicine, Department of Medicine at the University of Toronto, Canada.

Chapter 1
Prevention of HIV Infection

1.1 Introduction and Background

The global prevalence of infection with the human immunodeficiency virus [HIV] has been progressively increasing over the years from 8.5 million in 1990 to 35 million in 2013 [1], as a result of progress in treatment and not from a public health failure. The advent of combination of highly effective antiretroviral therapy [ART] has resulted in dramatic decline in mortality and morbidity form acquired immunodeficiency syndrome [AIDS] in the last 20 years. Hence, people with HIV infection are living longer with lifespan approaching the general population. Despite this progress, there were still over 2 million cases of new infection globally in 2013 but this is an improvement as there were 3.5 million new cases in 2000 [1]. However, there is a demand for improved preventative measures. UNAIDS has called for the enhancement of preventative methods and indicates that 25% of global HIV spending should be directed for prevention [2].

1.2 General Non-pharmacological Measures

Soon after the discovery of HIV in the mid-1980s and the development of diagnostic tests, epidemiology investigations elucidated the means of transmission, and widespread public health measures were undertaken to reduce the risk of spread. These measures included: education of the general populations on the means of transmission through mass media; advocating safe sex with use of condoms for all sexual activity outside of marriages or long-term monogamous relationships; screening of all blood products for HIV by PCR and restriction of blood donations from high-risk groups, such as men who have sex with men [MSM] and injection drug users [IDU]; encourage use of clean needles with needle-syringe exchange programs and some countries

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institute safe, supervised drug injection free-standing sites. The impact of these methods in reducing the spread and transmission of HIV has been difficult to measure in terms of percentage efficacy, but there is no doubt that they limited the expansion of the HIV epidemic. Most countries of the world now have HIV-free blood supply and blood transfusion-related HIV is almost non-existent, and the risk of HIV infection after blood transfusion in most countries is almost zero.

How effective is safe sex in preventing transmission of HIV? Theoretically, condoms should be highly effective in preventing HIV and other sexually transmitted diseases. Condoms, in general, provide an effective barrier against microbial–mucosal contact to prevent the entry of microbes in the body through sexual activity. However, strict adherence for all sexual activity for high-risk groups has been a problem and accidents do occur, such as slippage or breakage of the condoms. A previous systematic review indicated that consistent use of condoms decreases HIV transmission by 80% [3]. However, there is evidence that the populations of many countries, especially adolescents, young adults, and MSM, have resorted to practices of unsafe sex without condoms. This has been attributed to "consumer fatigue" from hearing the same message repeatedly on a chronic basis. In the USA, where MSM account for nearly half of new HIV infections the practice of unprotected anal sex has been increasing, from 48% in 2005 to 57% in 2011 [4]. Moreover, 38% of HIV-infected gay men unaware of their HIV infection reported unprotected sex. Hence, universal voluntary HIV testing with the immediate institution of ART for those positive has been advocated for the elimination of HIV transmission [5].

Other non-pharmacological method advocated to reduce sexual transmission of HIV includes male circumcision. A meta-analysis of three randomized controlled trials of male circumcision, reported a 54% reduction in HIV transmission from heterosexual sex in circumcised men versus non-circumcised males [6]. Whereas, circumcision in homosexual men who practice primarily insertive anal sex the effect of circumcision was greater, 73% reduction in the risk of HIV infection in the negative partner [7]. Evidence also suggests that interventions such as providing a free supply of condoms and clean needles can be effective in decreasing HIV transmission [8].

1.3 Prevention of Perinatal HIV Transmission

Prevention of mother-to-child transmission of HIV is a major success story that has been achieved in the last 20 years. Prior to intervention measures, perinatal transmission averaged 25% but is now <1–2% with ART prophylaxis and almost zero in wealthier countries [9]. Women account for 57% of people living with HIV in the most profoundly affected region of the world, sub-Saharan Africa, where six countries have HIV prevalence rates above 10% in 2015: Botswana, Lesotho, Namibia, Swaziland, South Africa, and Zimbabwe [10]. Reduction of maternal-infant transmission of HIV was first demonstrated with zidovudine [ZDV] monotherapy by 67% in African women in 1994 [11]. Treatment was given during the second and third trimester of pregnancy, at delivery, and in the perinatal period. Most of the risk

of transmission occurs after 36 weeks and especially intrapartum, but breast-feeding also carries significant risk with the highest rate within the first 4 weeks and 8.9 per 100 child years afterward [12, 13]. In low- and middle-income countries, it is not uncommon for pregnant women to present at term in labor without any antenatal care, and single dose ART, nevirapine [NVP] or lamivudine [3TC]/ZDV, with neonatal therapy has been shown to reduce the risk of HIV transmission but not optimally [14, 15]. In this circumstance, the cesarean section with prophylaxis can reduce the risk of perinatal transmission even further. A meta-analysis of 15 prospective studies has confirmed the benefit of cesarean section over vaginal delivery [16]. Elective cesarean delivery before the onset of labor and short-term ZDV may decrease transmission of HIV below 1% [17]. However, cesarean delivery is usually recommended if the viral load is ≥1000 copies at or just before delivery. Longer use of a potent combination of ART, from the initial recognition of pregnancy, has resulted in progressive decline of perinatal transmission of HIV, to virtual elimination if ART is started even before conception. It was initially considered that ART should be started after 14 weeks of pregnancy, to limit any teratogenic effect of the treatment, but birth outcome has been reassuring with no overall significant increase in birth defects with initiating ART in the first trimester. There is controversy regarding the risk of central nervous system abnormalities associated with efavirenz in the first trimester of pregnancy [18], which was usually avoided because of fetal defects in animal experiments, and exposure to ZDV in the first trimester has been reported to cause an increase in congenital heart defects [19]. Poor growth outcomes at 5 years have also been reported with perinatal exposure to ZDV or NVP [20].

Based on a model of hypothetical cohort of 100 children born to HIV-infected women without any intervention, the risk of perinatal transmission in early pregnancy had been estimated to be <5% [21], but even this small risk is worth eliminating and the risk of adverse neonatal outcome has to be carefully considered with the use of early ART. Preterm delivery and low birth weight have been reported with several ART regimens in pregnancy, even when started after 14 weeks and these include NVP-based, protease inhibitors [PIs] and tenofovir [TFV]-based combinations [22–24]. In a recent reported trial in African pregnant HIV-infected women, with median CD4 count of 530 cells, enrolled at a median of 26 weeks gestation, women were randomly assigned to one of three regimens: ZVD alone with intrapartum NVP, ZVD/3TC or lopinavir/ritonavir [LPV/r] and TFV/emtricitabine [FTC]/LPV/r [24]. The rate of perinatal transmission was significantly lower in the ART combination than ZDV alone [0.5% versus 1.8%]. However, TVF-based ART was associated with greater preterm delivery before 34 weeks [6.0% vs 2.6%, $p = 0.04$] and early infant mortality [4.4% vs 0.6%, $p = 0.001$] than ZVD-based ART.

The World Health Organization [WHO] in 2010, recommended lifelong ART for women with CD4 counts ≤350 cells/μl or in WHO clinical stage 3 or 4, and short-term prophylaxis during pregnancy after 14 weeks for women with higher CD4 counts [25]. Option A was to continue NVP in the infant while breast-feeding, and Option B was to continue ART in the mother throughout breast-feeding. However, testing CD4 count is recognized as a barrier in African countries to initiate lifelong ART and prevent mother-to-child transmission. With a high HIV prevalence, limited

laboratory facilities and practice of extended breast-feeding, the Malawian Ministry of Health adopted a pragmatic approach and offered all pregnant women lifelong ART irrespective of CD4 cell count and clinical stage [26]. Due to international interest, 2013 WHO guidelines recommend lifelong ART for all pregnant and breast-feeding women [27]. Most industrialized countries now recommend starting ART as soon as the diagnosis is made irrespective of CD4 count, thus most women should be on ART preconception and continuation of therapy in early pregnancy. How safe is ART in the first trimester of pregnancy? No randomized, controlled trial has been published to date to directly address this issue. However, the analysis of data from the French Perinatal Cohort, which included 8075 infants born to HIV-infected women from 2000 to 2011, has provided important insights [9]. No perinatal transmission occurred in 2651 infants whose mother started ART before conception, continued treatment during pregnancy and had a viral load <50 copies/mL at term near delivery. Starting ART later in pregnancy and a viral load >50 copies/mL were independent risk factors for perinatal transmission. When ART was started in the first trimester of pregnancy it was nearly as good as when started before pregnancy. However, even with a viral load <50 copies/mL near the time of delivery a few perinatal transmission [14 infants in 2694 women or 0.5%] occurred, when ART was instituted in the second or third trimester. There were 16.1% preterm deliveries, higher than the general population, but most were moderate preterm between 32 and 36 weeks gestation. Preterm deliveries were similar in mothers who started ART before conception and those starting ART in the first two trimesters and lower in women initiating treatment in the third trimester [9]. Current guidelines in North America and most western European countries recommend starting ART in all HIV-infected women before conception or, if they are already pregnant, to start as soon as possible [https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGLpdf].

1.3.1 Breast-Feeding and HIV Transmission

Prior to the availability of ART for breast-feeding mothers on the maintenance of NVP prophylaxis in breast-fed infants, it was calculated that breast-feeding carried a 16.2% risk of HIV transmission [28]. Others have calculated that the cumulative probability of late postnatal transmission from breast-feeding at 18 months was 9.3% [29]. Breast-feeding has major benefits to the infant [and to a lesser degree the mother] it provides physiological, psychological, nutritional, and immunological advantages over formula feeding. Earlier clinical trials had shown that infants in Africa, randomized to breast-feeding plus ZDV or formula feeding for 6 months, had higher rates of HIV infection with breast-feeding but significantly lower cumulative mortality [30]. Furthermore, other studies had reported that early weaning from breast-feeding in Africa increased diarrhea mortality and morbidity among uninfected infants born to HIV-infected mothers [31].

Clinical trials in Africa have also shown that extended maternal triple ART or infant NVP prophylaxis for 28 weeks during breast-feeding can reduce HIV transmission

from 5.7% in the control group to 2.9% in the maternal ART group or 1.7% in the infant NVP group at 28 weeks; and at 48 weeks the respective rates were higher [7% vs 4%] but still significantly lower in the treated groups [32]. However, infant prophylaxis for the full duration of breast-feeding with LPV/r or 3TC had demonstrated greater reduction of HIV transmission at 50 weeks to 1.4–1.5% [33]. With regard to infant feeding, the WHO guidelines recommend exclusive breast-feeding for 6 months and to continue for 12 months supplemented with foods, in low-income and some-middle income countries, where breast-feeding with ART intervention is preferred [27]. Intermittent breast-feeding is not recommended as it carries about double the risk of HIV transmission than exclusive breast-feeding [34]. Most industrialized countries recommend only formula feeding despite indefinite highly active third-generation ART; but should the guidelines be changed and give mothers the choice? A recent article has discussed this issue and argued convincingly that the approach should be based on shared decision-making regarding infant feeding with HIV-infected mothers, as this is ethically justifiable [35]. Recent studies in Africa, using older triple ART regimens with high pill burden and less tolerable than single pill, triple-drug regimens [commonly used in high-income countries], in breast-feeding mothers had reported HIV transmission well under 1% [36, 37].

1.4 Postexposure Prophylaxis for Percutaneous Exposure

1.4.1 Nonhuman Primate Studies

Postexposure prophylaxis with antiretroviral drugs to prevent HIV infection was first demonstrated in nonhuman primate models in the early 1990s. The simian immunodeficiency virus [SIV], which is considered very similar to HIV, was used to inoculate macaques intravenously and ZDV was given postinoculation. The protective efficacy reported with this agent was only 46–57%, odds ratio of 0.43–0.54 [38, 39]. Since then multiple studies have been performed from various countries. Irvine et al. recently reviewed 25 studies with 408 primates inoculated primarily intravenously with SIV or HIV [40]. The risk of seroconversion was significantly lower with postexposure prophylaxis [PEP] than in controls, 89% protection. A significant association was found between the timing of PEP and protection, the sooner the better, and TFV was more effective than other drugs studied. There was no evidence that the combination of agents was superior to single drugs, but the power of the combined studies may be insufficient to show a difference [40]. TFV was found to be fully effective 24 h after intravenous inoculation of SIV to prevent infection and administered for 4 weeks, but had reduced effectiveness when given 48 or 72 h postinoculation [41]. Shorter duration of PEP such as 10 days was also found to be ineffective. Limitation of these studies, as noted by the review, includes small sample sizes [which is usual with nonhuman primate studies due to high expense] and lack of randomization; also inoculum of virus used to ensure infection would be much higher

than in humans from percutaneous or sexual exposure of HIV. The strengths of the primate model for study of PEP, besides inability to conduct controlled randomized human studies because of ethical issues and huge sample size required, included: similarities in pathogenesis of SIV infection in nonhuman primates and HIV infection in humans; also similarities between humans and nonhuman primates in physiology and immunology; ability to control for virus strain and inoculum; ability to study the effect of timing of PEP after various time intervals postinoculation; and [as with all experimental animal models] the ability to assess for early clinical manifestations and readily confirm the outcome and pathology [40].

1.4.2 Postexposure Prophylaxis After Percutaneous or Occupational Exposures

Percutaneous exposure to HIV from needle-stick injuries [primarily deep injuries with hollow-bore needles] in health-care personnel was estimated to result in 0.3% risk of infection [42]. Previous attempt to conduct a national randomized controlled study of PEP with ZDV in the USA was abandoned due to low enrolment. Hence, a case-control study was performed with logistic-regression analysis based on 33 case patients and 665 controls and the use of ZDV for PEP [43]. Significant risk factors for seroconversion were deep injury [odds ratio {OR} 15], visible contamination of the source blood on the device [OR 6.2], procedure involving placement of the needle in the vein or artery of the source [OR 4.3], and exposure to a source patient who died of AIDS [OR 5.6]. Case patients were significantly less likely to have received ZDV PEP after the exposure [OR 0.19], for 81% protective efficacy [43]. The limitation of this study included the retrospective nature, small number of case patients and the potential for bias in reporting infected cases.

Exposure of mucous membrane to HIV-infected blood has been estimated to carry a risk of approximately 0.09% of HIV transmission [44]. The risk of transmission by infected blood with exposure to nonintact skin has never been calculated but is estimated to be less than the risk of mucous membrane exposure, but episodes of HIV infection has been documented with this type of exposure [45]. The HIV status of the source of any occupational blood exposure should be determined as soon as possible to determine the need for continued PEP, as PEP should be started soon after any credible blood exposure but not including the intact skin. Baseline blood tests including serology for hepatitis B and C and HIV are usually performed and a triple combination of ART is recommended by guidelines [45]. However, older combination of ART containing ZDV, stavudine [D4T], and didanosine [DdI] were not well tolerated. In an earlier study in 2000, 76% of health-care workers experienced some side effects to PEP and 43% did not complete treatment mainly because of the adverse effects of the drugs [46]. Fewer side effects were reported with two-drug PEP regimens than by three-drug combinations. Current PEP regimens with TFV-FTC-based combinations are much better tolerated. Previous guidelines had recommended follow-up serology

Table 1.1 Risk of HIV transmission by various routes

Exposure routes	Risk per exposure	95% CI	References
Parenteral exposure			
Cutaneous needle stick	0.23%	0.0–0.46%	[50]
Needle-sharing drug use	0.63%	0.41–0.92%	[51]
Mucous membrane			
Blood exposure	0.09%	0.006–0.5%	[44, 45]
Sexual exposure			
Insertive anal sex	0.11%	0.04–0.28%	[51]
Receptive anal sex	1.38%	1.02–1.86%	[51]
Insertive vaginal sex	0.04%	0.01–0.14%	[51]
Receptive vaginal sex	0.08%	0.06–0.11%	[51]
Receptive oral sex	Not calculable	0.0–0.04%	[52]
Vertical transmission			
Perinatal transmission	22.6%	17–29.0%	[5]
Breast-feeding	9.3–16.2%	NA	[28, 29]

CI confidence interval, *NA* not available

for up to 6 months, but the new guideline indicated that follow-up HIV testing can be concluded at 3–4 months [45].

1.5 Sexual Transmission of HIV and Nonoccupational Needle Exposure

The majority of HIV infection worldwide is attained through sexual transmission, mainly by heterosexual activity in high endemic countries, such as in Africa, and by male homosexual activity in industrialized countries, such as in North America. The risk of infection varies widely depending on the number of partners, type, and frequency of sexual activity, viral load of the partner, presence of ulcerative and nonulcerative sexually transmitted infections, and even the presence of bacterial vaginosis [47–49]. The risk of HIV transmission by various exposure routes is summarized in Table 1.1. A systematic review of HIV transmission per-act was recently published [51]. Overall, vaginal receptive sex per-act was associated with a 0.08% risk of transmission and anal receptive sex of 1.38%, but the risk may be significantly higher for a newly infected partner with high viral load, undiagnosed, or on no treatment. One study reported a higher risk of transmission with ejaculation with receptive anal sex compared with withdrawal before ejaculation, 1.43% versus 0.65% [53]. Insertive vaginal sex [0.04% per-act] and insertive anal sex [0.11%] have a lower risk of transmission than the receptive counterpart. There is no estimated risk for oral sex, which is considered very low but HIV transmission has been reported especially with receptive penile oral sex with ejaculation [54].

The risk of HIV infection from sharing needles among injection drug users [IDU] had been estimated to be higher than occupational needle-stick injuries, and one estimate was 0.4%–3% from an HIV-infected untreated person, depending on the viral load, but a mathematical model estimated an overall risk of 0.67% [55, 56].

Several studies have shown that high blood HIV viral load increases the risk of sexual transmission and there is a correlation between transmissibility of the virus, plasma viral load, and genital HIV-RNA quantity [57–60]. Heterosexual transmission has been reported to be rare in HIV discordant African couples with plasma viral load <1500 copies/mL [61]. Genital HIV-1 RNA quantity also independently predicted heterosexual transmission after adjusting for plasma viral load [61] and ART can suppress genital shedding of the virus [62]. The minimal infective dose for sexual transmission of HIV is unknown. However, in a prospective study of 2541 African HIV-1 serodiscordant couples genital HIV-1 RNA quantity and HIV transmission risk were assessed [61]. Each 1 $\log_{10}$ increases in genital HIV-1 RNA from endocervical swabs or semen was associated with a 2.2-fold and 1.7-fold increase in transmission, respectively. HIV-infected patients CD4 counts were >350 cells and were not receiving ART and 28.6% of couples reported unprotected sex. Among the HIV-negative partners, 113 seroconverted within 24 months and 69% were linked to the partnership. Transmission of HIV from female to male was associated with endocervical median RNA level of 3.89 $\log_{10}$ [7762] copies/swab versus in the non-transmitters 3.18 $\log_{10}$ [1513] copies/swab, $p < 0.001$. Similarly, male to female transmission was associated with a median HIV-1 RNA level of 3.44 $\log_{10}$ [2754] copies/mL of semen and non-transmission with 2.54 $\log_{10}$ [346] copies/mL of semen, $p < 0.001$. However, 11 HIV transmissions [<1%] occurred from persons with undetectable genital HIV-1 RNA but detectable plasma levels [61]. The major limitation of this study is that genital HIV concentrations were performed only once in the study subjects and variations in concentrations can occur and, therefore, higher genital levels of HIV could be easily missed.

Effective ART can suppress plasma and genital levels of HIV and halt transmission of the virus. However, some studies have found detectable HIV-RNA while receiving ART and with undetectable plasma viral load. In a prospective study of men starting ART, isolated HIV semen shedding was present in 19 of 116 [16.4%] samples in subjects with undetectable blood viral load, with high levels [6672–16,026 RNA copies/mL] in 5 of the 19 samples [63]. Since viral cultures of the samples were not performed it remains unknown whether or not the viral particles present in the semen were viable transmissible agents. The largest study of genital mucosal shedding of HIV was recently reported in a prospective sstudy of >1100 African women on ART [64]. Genital HIV-RNA was detected [median viral load 3.16 copies/swab] in 6% of >1400 visits by women with undetectable plasma viral load and 24% [median genital viral load 3.50 copies/swab] of about 400 visits by women with detectable plasma viral load. The factors associated with genital shedding of HIV were advanced disease, genital ulcers, and cervical tenderness. The presence of low genital concentration of HIV may not pose a significant risk of transmission for discordant couples, as a previous report indicated that approximately 14,000 sexual exposures did not lead to transmission despite detection of HIV shedding on ART [65].

1.5.1 Biology of Sexual HIV Transmission

Sexual transmission of HIV can be influenced by both host factors and viral conditions and transmission can occur with cell-associated or cell-free virions. In genital secretions of the donor a diverse viral population is present but in about 80% of cases, but only a single viral variant will establish infection [66]. The healthy genital tract provides multiple physical and immunological barriers that effectively blocks transmission in >99% of unprotected sexual exposures [67]. Present data suggest that transmission of HIV is characterized by many abortive events in which some target cells are nonproductively infected, and the transmitted founder virus is rarely the dominant variant but is selected by the underlying fitness of the virus [66]. Inflammation of the genital tract, regardless of the type of infection, increases the risk of HIV acquisition and may result in infection with multiple viral variants [68, 69]. Moreover, genital inflammation facilitates the transmission of less infectious virus, while highly infectious viruses are able to establish infection regardless of inflammation status [70]. Studies in nonhuman primates indicate that the minimal infective dose of SIV by the mucosal [genital] route is much higher than the dose required for infection by the intravenous inoculation and usually multiple genital inoculations have to be used [71].

Introduction of HIV into the genital tract results in rapid passage across the mucosal barrier, uptake of the virus by dendritic cells, and macrophages, then transported to regional lymph nodes within about 2 days of exposure [72, 73]. Dissemination of the virus to lymphoid organs/tissues all over the body by the bloodstream occurs within 3 days, to establish an irreversible infection [72]. Further studies in rhesus monkeys inoculated intravaginally with SIV, using a large inoculum of virus [2×10^9 copies of RNA], have provided more insights on the biology. Most of the virus is cleared by the mucosal barrier and only a very small founder population [several orders of magnitude lower than the inoculum] results in a productive infection of the genital tissues from 24 to 96 h postinoculation [74]. SIV-infected dendritic cells are rapidly conveyed to regional lymph nodes within 18–24 h of inoculation, but the continued expansion of infection at the portal of entry seems to be necessary for seeding to distal lymphoid tissues and to establish a productive infection. Although viral RNA could be detected in distal lymphoid tissues from 1 to 4 days postinoculation, there was little evidence of active replication until 6 days after inoculation [73]. The simian model indicates that systemic productive infection does not occur until day 3–6 postexposure, but the initial 72-h is considered the critical period to initiate PEP to prevent established infection.

1.6 Early ART for HIV Infection as Prevention

Initiation of effective ART as soon as the diagnosis of HIV infection is made, irrespective of CD4 cell count or clinical stage, has been shown to improve the quality and duration of life and reduce the infectious risk to the partners by several studies [75–77].

Early institution of ART in serodiscordant couples was found to prevent 96% of genetically linked HIV infection than delayed ART at 1.7 years [77]. Even after 5 years, early ART was associated with a 93% lower risk of linked partner infection than delayed ART [76]. A previous consensus statement by the Swiss Federal Commission for HIV/AIDS asserted in 2008, that people on effective ART [HIV plasma RNA <40 copies/mL] without genital infection could not transmit HIV by sexual contact [78]. This statement had raised much discussion and controversy. Other investigators using a mathematical model based on data from previous studies on HIV discordant couples, found that in heterosexual partnerships in the presence of effective ART, the risk of HIV transmission is very low but not zero [79]. Moreover, the transmission risk in male homosexual partnership is high over repeated exposures. The effectiveness of ART in reducing the risk of HIV transmission per sexual act was estimated to be about the same as reported for condoms. Therefore, even with ART in HIV discordant couples' condoms were still recommended. The estimated female to male transmission of HIV per-act was calculated to be 2.2×10^{-5} [about 1 in 45,000 risk]; male to female expected risk 4.3×10^{-5} [about 1 in 23,000]; and male to male expected risk 4.3×10^{-4} [about 1 in 2300] [79]. In a hypothetical population of 10,000 HIV discordant couples with plasma viral load <50 copies, in 1 year MSM could result in 282–352 new HIV cases and male to female couples 32–42 new infections [79].

A recent observational prospective study on serodiscordant couples, with the HIV-infected partner on suppressive ART [Partner Study], was conducted at 75 clinical sites from 14 European countries [80]. This study included 1166 couples, 888 heterosexual, and 340 MSM who were practicing condomless sex and the infected partner had HIV-RNA load <200 copies/mL. During 1.3 year follow-up, there was no documented case of within-couple HIV transmission, with an upper 95% confidence limit of 0.30/100 couple years of follow-up. Based on a median of 37 condomless sex act per year, the risk of HIV transmission was <1 per 22,000 acts in MSM and <1 per 36,000 acts with heterosexual partners [78], which are still consistent with the previously mentioned model estimates. In another recent study, a Bernoulli model was used to estimate the HIV sexual risk in serodiscordant couples with the effect of combining strategies [81]. In heterosexual couples with HIV-infected male partner the risk of transmission on ART was 0.2% at 1 year and 2% at 10 years; with ART and pre-exposure prophylaxis [PrEP], the estimated risk was 0.1% and 1%; and for ART and condoms, the risk was 0.05% and 0.5% for the same time periods. In MSM the rates were higher, on ART alone the transmission risk was 3% at 1 year and 25% at 10 years; for ART and PrEP it was 2% and 20%, and for ART and condoms 1% and 6% for the same time period. These estimates of the transmission risk on ART appear to be significantly higher than the observed rates of transmission in the Partner Study [80, 81].

Current data clearly shows that effective ART markedly reduces the risk of HIV transmission but the risk is not near zero. Moreover, many patients that are well controlled have an episodic spike in their viral load associated with common upper respiratory infections or no clear reasons and may have increased transmission at these times. In addition, measurement of the cumulative viral burden in the treated HIV population may provide a better index of HIV transmission in the local community. In a study in the USA, using data from the National HIV Surveillance

System 238,641 patients in HIV care had at least two viral loads in 2012–2013. Approximately 62% of patients had durable viral suppression and 38% had high viral loads >1500 copies/mL [associated with increased transmission] for 316 days over 2 years [82]. Thus, improved retention in medical care and medication adherence are needed to greatly rely on ART to stem the tide of the HIV epidemic. It is also likely that in low- and medium-income countries with higher rates of HIV, that compliance, retention in medical care, and durable HIV suppression are even lower.

1.7 Postexposure Prophylaxis After Sexual Exposure

PEP after high-risk sexual exposure has been recommended since the 1990s [83], based on data from needle-stick injuries in health-care workers and nonhuman primate studies with intravenous inoculation. No randomized controlled studies were ever performed because of ethical issues and the huge number of subjects that would be required to show a significant difference. Also no case-control cohort studies were ever done. A subsequent study in pig-tailed macaques was performed after intravaginal inoculation with HIV-2 to assess the effect of PEP with TVF at different time intervals postinoculation [83]. A large inoculum of 10^5 tissue culture infectious doses [given as three divided inoculum over 2 h] was required to produce a 75% infection rate in control animals. None of 8 animals treated with TVF by 36 h postinoculation developed an infection, while delayed treatment at 72 h was ineffective [similar to controls] [84]. This study reinforced the recommendation to administer PEP as soon as possible and <72 h after the exposure.

How effective is PEP for high-risk sexual HIV exposure in preventing transmission? This is difficult to answer as there is no adequate data to address this issue. In a nonrandomized prospective study of nonoccupational PEP for HIV, 702 exposed persons were evaluable after 12 weeks for seroconversion [85]. Seroconversion was detected in seven subjects [1% 95% CI = 04%–2%] but only three cases most likely had PEP failure, as three seroconverters continued to have unprotected sexual contacts after PEP and one subject baseline HIV-RNA was detectable. All subjects received 28 days of dual nucleosides, ZDV/3TC, D4T/3TC, or DdI/D4T. However, only four subjects had excellent adherence to PEP and the three cases with likely PEP failure initiated therapy >45 h after exposure. This suggests that earlier institution of PEP is most important, moreover, animal experiments suggest that TVF combinations are more effective than older combinations. Completion rates with older ART combinations have been reported to be low before but new dual or triple combinations in a single pill are better tolerated with improved adherence. In a recent study from Australia, 100 HIV-exposed MSM given a single tablet of TFV/FTC/rilpivirine [marketed as Complera] reported 92% completion rate of the 28 days PEP [86]. No participant had HIV seroconversion. In a recent systematic review of adherence to postexposure PEP, the overall adherence to 28 days of therapy was only 56.6%, greater for nonoccupational exposure [65.5%] and MSM [67.2%], and was

especially low for adolescents [36.6%] and sexual assaults [40.2%] [87]. Unfortunately, this review did not analyze adherence according to the different types of combinations used for PEP. Starter packs for 2–5 days are commonly initiated, especially by emergency physicians, until the exposed subjects are assessed by an expert to decide on the need for continuation and side effects to the PEP. A systematic review of the use of starter packs versus full prescription from the outset found lower adherence and completion rates with starter packs [88]. However, based on my personal experience, the use of starter packs is likely safer and more cost-effective.

Recommendations for PEP in nonoccupational HIV exposures were for high-risk exposures after a detailed history of the exposure within 72 h. These included: unprotected anal or vaginal intercourse, receptive oral intercourse with ejaculation, or the sharing of needles with an HIV-infected person; for persons of unknown status and the source contact is available treatment can be started and stopped if the partner is HIV negative [83]. When the partner is unavailable or unwilling to be tested, treatment with PEP is based on the type of exposure and likelihood of HIV infection in the partner. For victims of sexual assault and rape PEP is routinely recommended. High-risk groups but unknown HIV status for PEP include: MSM, IDU, commercial sex workers, multiple sexual partners, former prisoners, subjects from high endemic regions: sub-Saharan Africa, South America, South East Asia, Caribbean, and former Soviet Union [89]. PEP was not recommended for subjects who continue their high-risk behavior and request PEP on multiple occasions, and they may be more suitable for PrEP. Based on current data, PEP should not be indicated if the partner was on ART and has undetectable viral load. A summary of the indications for PEP is shown in Table 1.2. Previous guidelines for PEP had recommended two-drug combinations and to use three drugs for exposure to a source patient with advanced AIDS and high viral load [84]. More recent guidelines have recommended three-drug combinations including TVF/FTC that are well tolerated [88]. It is unclear whether or not this is based on studies that show triple-drug combinations [with two nucleosides] were superior to dual drug combinations in advanced HIV-infected patients [90, 91]. The WHO acknowledges that two-drug ART combinations are effective for PEP but consider three dugs preferable [for unclear reasons], with LPV/r or atazanavir [ATV]/r as the preferred third drug [92]. Simplification of the guidelines for all HIV exposures and PEP was mainly to improve institution of treatment and adherence.

1.8 Pre-exposure Prevention of HIV

1.8.1 Topical Microbicides for PrEP

Self-application of topical microbicides intravaginally to prevent mucosal HIV infection has been considered a viable option in the overall attempt to limit the spread of the epidemic. Studies in nonhuman primates had provided support for this approach

but with variable success depending on the agents studied. In vitro and in vivo studies had shown that 1% gel of TFV was a potential topical microbicide to prevent HIV infection [93]. Furthermore, in monkey experiments, TFV gel given intermittently and with a single dose pre-exposure could prevent HIV infection [94]. In addition, rectal instillation of TFV gel 2 h before rectal inoculation of SIV produced a significant but partial protective effect [95]. Surprisingly, TVF gel provided a 75% protection against TVF-resistant SHIV inoculated intravaginally [96]. A phase IIb clinical trial with 1% TFV gel ion South Africa [CAPRISA 004] demonstrated that the overall protective efficacy was only 39% and 54% in women who used the gel more than 80% of the time [97]. In a more recent phase III trial in South Africa [FACTS 001], efficacy with TFV gel could not be proven because of poor adherence but a subgroup analysis of highly adherent women demonstrated about 55% efficacy [98]. Thus, daily or coital-dependent topical microbicide has very low adherence in African women. Hence, ART containing vaginal microbicide rings, which release medication over a month or longer, may have greater adherence and efficacy.

Intravaginal ring eluting TFV has been shown to completely protect macaques from multiple vaginal SHIV challenges, and this device protects the primates even after high-dose progesterone and multiple SHIV exposures [99, 100]. A novel pod-intravaginal ring [IVR] formulation delivering a combination of TFV/FTC with a sustained release over 28 days has been developed. In a recent study, all control macaques developed an infection with four inoculations of SHIV but all treated animals with the pod-IVR were protected [101]. Clinical trials with eluting IVR are warranted and compliance may be better than with topical gels. Recently, a phase III, randomized, double-blind, placebo-controlled trial with dapirivine, a non-nucleoside ART, IVR has been conducted in 1995 African women [102]. The dapirivine-IVR was replaced every 4 weeks for 2 years and was safe but no more effective than topical gels, with only a 31% protective efficacy relative to placebo [102]. In a similar trial among African women, dapivirine-IVR reduced HIV infection overall by 31% but in 37% with the exclusion of non-adherent women [103]. The rate of non-nucleoside reverse transcriptase inhibitor [NNRI] resistance in HIV-infected subjects was similar between the treated and nontreated groups. It will be interesting to learn whether or not TFV/FTC pod-IVR is any more effective.

1.8.2 Oral PrEP in MSM

Animal experiments in nonhuman primates had demonstrated that intermittent or continuous TVF alone or TFV/FTC could prevent SIV or SHIV when challenged with multiple low doses of viruses genitally [104, 105]. However, repeated high inoculum [fivefold higher than found in human semen of acute HIV infection] eventually caused delayed breakthrough infection [106]. Surprisingly, a lower risk reduction with prophylaxis was found with vaginal challenges than with rectal inoculation [105]. Coitally dependent prophylaxis [one dose 24 h before and a second dose 2 h after vaginal challenge] with TFV/FTC has been shown to be protective in macaques

Table 1.2 Indications for postexposure prophylaxis [PEP]

Types of exposure	Recommend	Consider
Needle stick		
HIV+, VL >50 copies	Yes	
HIV+, VL <50 copies		Offer
Unknown source		Offer
Sharing needle syringe		
HIV+ source	Yes	
Unknown HIV	Yes	
Mucous membrane		
Blood from HIV+ source	Yes	
Blood from unknown HIV		May offer
Body fluids: Semen, CSF etc.	Yes	
Saliva, urine, vomitus, tears	No	No
Sexual exposure		
Anal receptive	Yes	
Anal insertive	Yes [high-risk source]	
Receptive vaginal	Yes [high-risk source]	
Insertive vaginal	Yes [high-risk source]	
Receptive penile oral	Yes [high-risk source]	

Data obtained from references [27, 45, 87, 159–161]
Exposures within 72 h from source with HIV or potentially infected
High-risk groups: MSM, IDU, sex workers, multiple sex partners, former prisoners, from high-risk regions: sub-Saharan Africa, South America, Caribbean, South East Asia, and former Soviet Union

against SHIV [107]. In a more recent animal study, coinfection with *Chlamydia trachomatis* or *Trichomonas vaginalis* modestly decreased the protective efficacy pre-and post-challenge with TVF/FTC [108].

Continuous oral PrEP was first demonstrated to be effective as a fixed combination of TFV/FTC [Truvada] in MSM in 2010 [iPrEx trial], with an overall protective efficacy of 44% but up to 92% in fully adherent subjects [109]. By 2012 Truvada for PrEP was approved by the US Food Drug Administration for high-risk population and is now covered by most health insurance plan. The efficacy of this oral PrEP was confirmed to be close to 100% in the iPrEx open-label extension study in transgender women and MSM [108]. In an open-label randomized PROUD trial PrEP with Truvada daily immediately versus 1 year delay prevented 86% of HIV infection in MSM who practiced anal sex without condoms [110]. Daily PrEP has to be taken >70% of the time to be highly effective and overall is quite safe with rare occurrence of mild reversible renal impairment, and low risk of decreased bone density and acquiring drug-resistant HIV [111]. Observational data in several US cities with daily PrEP in MSM with managed health-care plan have shown high protective efficacy >90% in clinical practice [112, 113]. Despite the high efficacy of PrEP with daily Truvada in MSM shown in affluent countries, there has been a low utilization of this prophylaxis in the USA. In a recent survey of MSM who were sexually active and HIV negative in 20 US cities, only 5% were using PrEP but 50% would be willing to

take PrEP [114]. Similarly, in Atlanta it is estimated that only 15% of MSM are projected to achieve protection from HIV with daily PrEP due to multiple barriers [115]. These barriers to PrEP include: lack of awareness, risk/benefit perceptions, perceived side effects, cost issues without drug insurance, inadequate health-care access, and lack of a primary care physician. Current cost of PrEP in the USA is about $12,000 per year, thus it is primarily used by persons with drug coverage through insurance. Cost-effectiveness analyses of PrEP in MSM have provided varying estimates of the overall value. In a recent analysis of PrEP in MSM from Los Angeles County, PrEP was estimated to be highly cost-effective at $27,863 per quality-adjusted life years [116]. However, different conclusions were reached by others of the impact in New York, where it was estimated that PrEP prioritization in MSM would result in only 19% reduction of new HIV infections and would be relatively cost-inefficient and unlikely to be cost-saving [117]. Others have also reported that PrEP in MSM would cost US $160,000/quality-adjusted life year gained [118]. It was previously estimated in 2012 that PrEP in the high-risk MSM US population annual expenditure would exceed $4 billion, based on a daily cost of $25.86 [119]. Current daily cost of this fixed combination pill in the USA is $52.20 [according to Gilead] or $67.89 [according to a pharmacy in Detroit], and $29 [Canadian] in Ontario, Canada. Hence, upscale use of this PrEP in high-risk MSM could presently cost over 8–10 billion dollars annually in the USA.

Perhaps taking PreP intermittently and as needed would be more cost-effective, as the drug acquisition cost would be much lower. Animal experiments have shown this to be effective in preventing SHIV infection. A recent multicenter placebo-controlled, randomized trial in Canada and France in MSM [IPERGAY study], showed on-demand prophylaxis with Truvada produced 86% reduction of HIV infection in the treated group versus placebo in <12 months [120]. Two pills of the fixed combination or placebo were taken 2–24 h before sex, followed by a third and fourth pill 24 and 48 h after the first drug intake. In case of multiple consecutive episodes of sexual intercourse, the subjects took one pill per day until the last sexual contact and then two pills postexposure. The result of this trial is comparable to the efficacy of daily PrEP reported in MSM. A study of the social sexual behavior of MSM found that men were better at predicting not engaging in sex within the next 24 h than the likelihood of having sex, thus for PrEP on demand the dose could be taken unless there was no chance of sex in the next 24 h [121]. Further larger and longer trials are needed for PrEP on demand for high-risk heterosexual exposures and intravenous drug exposures.

1.8.3 Oral PrEP in Heterosexuals and Drug Abusers

PrEP may also be considered for people who inject drugs [PWIDs] and at risk for HIV infection, primarily IDUs who share needle and or other paraphernalia used in the preparation and administration. The only randomized, controlled trial in this group [the Bangkok Tenofovir Trial] used TVF as a single agent [122]. Daily oral TVF

resulted in an overall 48.9% reduction of HIV infection and 74% protection in those with detectable TVF concentration. This trial enrolled 2413 people and improved adherence was associated with lower HIV infection, over 97% adherence to PrEP resulted in 83.5% protection against HIV infection [123]. In this study sterile needles could not be provided to participants [Thai law], thus the added benefit of the recommended practice of needle and syringe exchange programs could not be determined.

Randomized, controlled, clinical trials of daily oral PrEP in high-risk heterosexuals have been performed primarily in sub-Saharan Africa with mixed results. In the first study, 4747 HIV discordant couples were randomized to TFV alone, TFV-FTC or placebo for 36 months [Partners PrEP study] [124]. The protective efficacy of TFV-FTC [75%] versus TVF alone [67%] was not significantly different, but both prophylaxes were significantly effective compared to placebo [$p < 0.001$]. As an extension of the Partners study, 1013 HIV discordant couples in Kenya and Uganda were enrolled in a prospective implementation study from 2012 to 2015 [125]. PrEP [TFV-FTC] was given until 6 months after ART initiation of the HIV-infected partner. Over the 3 years, only two incident HIV infections occurred, with an observed incidence of <0.5% per year compared to an expected incidence of >5% per year [125]. The TDF2 study from Botswana, with the prevalence of HIV infection of 17.6% overall, enrolled 1219 HIV-negative sexually active men and women to receive daily TFV-FTC or placebo [126]. TVF-FTC was 62.2% effective in preventing HIV infection after a median of 1.1 years. Two other randomized controlled studies of daily PrEP in African women failed to show any protective efficacy against HIV infection. In the Fem-PrEP study, 2120 HIV-negative women from Kenya, South Africa, and Tanzania received either TFV-FTC or placebo [127]. Drug adherence was low and no benefit of PrEP was found but with some increase in side effects [4.7% versus 3.0%]. A more recent study [Voice] enrolled 5509 sexually active women of reproductive age from South Africa, Uganda, and Zimbabwe to receive daily prophylaxis with TFV, TFV-FTC, 1% TVF vaginal gel or placebo [128]. None of the drug regimens reduced the rate of HIV infection but adherence to study drugs was low, with 25% to 30% having detectable TFV. From the results of these trials, it is quite evident that PrEP efficacy is largely dependent on strict adherence to the regimen. A summary of the pre-exposure measures to prevent HIV infection is shown in Table 1.3.

1.9 Prospects of Future Effective HIV Vaccine

An effective and safe HIV vaccine is a global priority and would be a major advance in the battle to control HIV infection and prevention of AIDS. Several vaccines have been tested for efficacy in humans, but only one produced modest [31%], transient protection against HIV infection [129]. This RV144 trial in Thailand used a canarypox vector expressing HIV genes as a prime, followed by two booster injections of a recombinant HIV envelope glycoprotein. IgG antibodies against the V1V2 region of the HIV envelope proteins were associated with reduced infection

[130]. Plans are underway to improve the results of RV144 by using multiple boosts, modified vectors, and adjuvants in a trial in sub-Saharan Africa [131]. Development of an effective vaccine to produce sustained humoral and cellular immunity at the mucosal level to prevent HIV entry into the body and to generate high circulating neutralizing antibodies has been a giant challenge. Intranasal delivery of a vaccine could induce the first line of defense at the mucosal level. Studies in nonhuman primates with Sendai virus [SeV] carrying SIV genes demonstrated protection against SIV challenges [132]. A preclinical human study with a replication-competent SeV-vectored HIV-1 Gag vaccine found intranasal administration produced functional, durable HIV-specific T cell responses and boosted antibody responses [133].

Antibodies that neutralize HIV-1 are found only in a small fraction of infected persons and most HIV-infected people produce non-neutralizing antibodies or antibodies that neutralize a limited number of HIV strains. However, so far the development of a potent HIV vaccine that can stimulate high and durable broadly neutralizing antibodies [bNAbs] has been elusive. Understanding the reason for the failure of natural HIV infection to generate neutralizing antibodies to clear the virus may be a key factor in vaccine development. In other viral infections, if the patient survives acute infection, neutralizing antibodies develop that clears the virus after days–weeks and provide lifelong protection from reinfection with the same virus. A minority of HIV-infected patients [about 20%] develop bNAbs after 2–3 years which are capable of neutralizing multiple strains of HIV, except the patient's own circulating strain [134]. To date, there are more than 100 bNAbs described. These bNAbs target one of four sites on the virus envelope glycoprotein, CD4-binding site, a glycan patch surrounding the V3 loop, apex of the HIV-1 spike and gp41 [135].

Isolation of bNAbs from infected patients with high levels of HIV-1-neutralizing serum activity [called elite neutralizers] was achieved with single-cell-based anti-HIV-1 antibody cloning techniques [136]. Generation of bNAbs, some of which can neutralize up to 90% of HIV strains at low concentration, are in clinical development and could be used for prevention or immunotherapy [137]. Studies have shown in monkeys that a single injection of four anti-HIV monoclonal antibodies prevented SHIV infection, even after 23 weekly challenges [138]. However, there would be limited need or application for passive immunotherapy for HIV, in general. Development of antibody-resistant virus to broadly neutralizing HIV-specific monoclonal antibodies is also a roadblock, but it was recently shown that an antibody that blocks the virus-binding site on human CD4+ T cells could induce sustained virologic suppression without inducing resistance in HIV-infected persons after treatment interruption [139].

Intensive research is ongoing to develop a vaccine that can generate high levels of bNAabs. Development pathway toward an effective vaccine has been described by Fauci et al. [140]: (1) defining the correct target on the virion, epitopes in the region of the trimeric heterodimer of the envelope are considered the most promising sites; (2) delineation of the targets, conformations of the relevant regions have been delineated; (3) engaging B cells in the bone marrow and lymphoid tissue through a process called B-cell lineage immunogen design; (4) using recombinant technology, members

Table 1.3 Pre-exposure preventative measures for HIV infection

Method	Efficacy	Cost-efficiency	Comments
Non-pharmacological Methods			
Condoms	80%	High	Inexpensive
Circumcision			
Heterosexual sex	54%	Moderate	Not calculated
MSM	73%	Moderate	Not calculated
Needle/syringe exchange	NA	Likely efficient	Not calculated
Pharmacological methods			
Topical microbicide	0–54%	Low-moderate	Low adherence
Vaginal ring	27–37%	Low-moderate	Low adherence
Daily oral PrEP			
MSM	44–92%	Low	Expensive
Discordant couples	67–75%	Low?	Not calculated
IDU	48–74%	Low?	Not calculated
Women in Africa	0%	None	Low adherence
PrEP on demand	86%	Moderate?	Not calculated

of the lineage must be expressed to identify virion envelope epitopes that bind most avidly; (5) these epitopes must be converted into immunogens and integrated into a vaccine strategy, likely in a prime-boost manner, to involve naïve B cells and stimulate hypermutations toward bNAbs responses. Most experts in the field of HIV vaccinology contend that an effective vaccine regimen must include both a B-cell vaccine for inducing bNAbs and a cell-mediated vaccine to induce strong CD8+ T cell responses. One such vaccine candidate may be composed of HIV genes inserted into a cytomegalovirus vector, similar to the SIV vaccine which resulted in viral clearance in 50% of nonhuman primates tested [141].

1.10 Viewpoint and Future Directions

Controversy over ART therapy for pregnant women with HIV was generated by a systematic review and meta-analysis which concluded that ZDV/3TC containing combination should be used instead of TFV/FTC combinations, because of increased stillbirths/early neonatal deaths with the latter [142]. This conclusion was largely based on one trial [thus data not robust] and the investigators of that study disagreed with the conclusion of the review. Furthermore, the US Panel on Treatment of Pregnant Women with HIV Infection and the British HIV Association did not support the recommendation to use ZDV/3TC over TFV/FTC in pregnancy, and I fully endorse their stand [143]. More recently, a prospective observational study found that maternal TFV containing regimens did not adversely affect perinatal outcomes [144]. In addition, recent data from two US-based cohort studies of 4646 birth outcomes found no increased risk of adverse birth outcomes with

TFV/FTC versus ZDV/3TC containing combinations [145]. In recent years, the WHO has recommended a highly effective triple combination containing TFV/FTC and dolutegravir [integrase inhibitor] as first-line therapy for HIV infection [women and men]. However, recent observational collected data from Botswana showed an increased risk of congenital neural tube defects with dolutegravir compared to other ART during the first trimester of pregnancy [3/1000 versus 1/1000 deliveries] [146]. Thus, it may be best to avoid this combination in women of child-bearing age not on birth control, as the greatest risk is in the first 8 weeks of pregnancy.

A multipronged approach is clearly needed to prevent HIV infection and end the persisting pandemic. Methods of prevention will depend on the population being targeted unless an effective vaccine can be developed that can be given to all at risk groups and populations. However, an effective vaccine may take many years to develop if ever designed. In the meantime we have to maximize the preventive regiments currently available which should be individualized to match the needs and ability of the individuals to afford.

It is this author's viewpoint that routine screening of all at risk subjects every 6 months and immediate institution of ART is the most cost-effective preventive method that should be adopted globally in all countries. Regular use of condoms and circumcision should still be advocated but triple-drug combinations for PEP are unnecessary and costly. Truvada alone should be used for PEP just as it is used for PrEP. Triple-drug combinations of ART are highly effective for HIV infection and AIDS, where there are multiple millions/billions of viruses in the body. Whereas, with sexual exposure subjects are exposed only to several thousand copies of the virus. Guidelines that recommend triple drugs for PEP have limited its use to those with drug insurance coverage and the wealthy. In a similar vein, daily PrEP for short term [<5 years] may be cost-effective in MSM but not does appear to be cost-effective for longer term [10–20 years]. Hence, it would be more cost-effective to advocate the use of PrEP on-demand, which is less expensive and more affordable.

Recent observational studies in young MSM have shown a progressive decline in adherence to daily PrEP after week 24, as only 34% of participants had blood levels consistent with >4 pills/week at 48 weeks and >80% practiced condomless sex [147]. Moreover, in adolescent MSM only 22% of subjects had protective blood levels of Truvada at 48 weeks [148]. Thus daily PrEP on a long-term basis even in North America will not reliably decrease transmission of HIV. Whether long-acting PrEP by injection every 1–3 months will be more effective after a year is to be seen.

Future trials for PrEP in heterosexuals and especially high-risk women in Africa, with long-acting injectable ART are already being implemented and the results are being awaited. These drugs can be given every 4–8 weeks and have shown protection in SHIV monkey models [149, 150]. This may improve the adherence in women compared to daily PrEP but it is doubtful that high compliance can be achieved over many years. Other potential method of delivering long-acting drugs for PrEP being investigated includes subcutaneous implants with slow-release drugs that can provide year-long protection, similar to subcutaneous implants for contraception.

The UN General Assembly in 2014 proposed to achieve 90% reduction in HIV incidence by 2030 compared to the level in 2010 [151]. This was based on achieving a global HIV 90-90-90 target; aiming to have 90% of people with HIV aware of their status, 90% of people with HIV on ART, and 90% of people on treatment with suppressed viral load by 2020. However, a recent study using a mathematical model suggests this will be almost impossible to achieve and more likely represent a pipe dream. Based on calculations using the most optimistic aims, 95-95-95, 2–4 tests per year of high-risk MSM, 100% PrEP for high-risk subjects, and 100% MSM condom use, only an 80% reduction would be possible by 2030 [152]. Although this would still be a major achievement, it appears that even this target would be unattainable.

1.11 Concerns

Since the advent of daily PrEP many MSM has abandoned the use of condoms for safe sex and may be more indifferent and promiscuous, due to the belief that they are safe from HIV infection. In a recent review of eight studies with a total of 4388 participants, PrEP use was associated with an increased prevalence of rectal chlamydia and any sexually transmitted infection [STI] diagnosis [153]. This observation also reflects the increasing incidence of STI seen in North America, including syphilis. Although guidelines recommend regular screening for STI in subjects on PrEP and most STI are easily treatable, the increasing antibiotic resistance of *Neisseria gonorrhea* is becoming a problem and will be fueled by this trend. In addition, PrEP in MSM leads to condomless sex that increases the risk of sexually acquired hepatitis C infection [154]. Also at least three cases of multidrug-resistant HIV-1 infection have been reported in MSM adherent to PrEP [two in North America and one in developing country], and there are likely more unreported cases [155]. Furthermore, black MSM who make up 40% of new HIV infections in the USA have low use of PrEP [10% of PrEP use in 2016], with low adherence and high discontinuation rate which will fuel the rate of multidrug-resistant strains of HIV [156]. PrEP so far has not been proven to reduce HIV infection at the population level, whereas universal testing early implementation of ART was recently shown to reduce the population-level incidence of HIV by 30% [157].

It is also unclear whether or not indefinite long-term use of PrEP is superior, more cost-effective and results in greater well-being, than assiduous safe sex practice and HIV testing every 6–12 months with prompt institution of ART for those positive. Taking one pill of oral PrEP is not much different from taking a single combination of three antiretrovirals in HIV-infected patients. MSM who adhere to daily PrEP [>90%] is evidently more health-conscious and a long-term study over 10 years may be feasible to compare these two strategies for prevention, cost-effectiveness, and clinical-effectiveness. However, in 10–20 years there is a slim possibility of curative treatment for HIV infection. A glimmer of hope on the road to curing HIV has been raised by a recent study in HIV-1

infected humanized mice by sequential long-acting slow-release antiviral therapy [LASER ART] and eradication of latent proviral DNA by RNA-directed gene editing technology [CRISP-Cas9] [158]. In this study, 2/7 mice eliminated integrated HIV proviral DNA from blood, lymphoid tissue, bone marrow, and brain. However, this study should be reduplicated by other investigators and should be applied to nonhuman primate model.

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Chapter 2
Immune Reconstitution Inflammatory Syndrome and Paradoxical Reaction

2.1 Introduction

Shortly after the introduction of highly active antiretroviral therapy [ART] for the acquired immunodeficiency syndrome [AIDS] and human immunodeficiency virus [HIV], a paradoxical inflammatory condition was described in some patients being treated for opportunistic infection, and not due to failure of treatment or resistance, during early improvement in the immunity and was called immune reconstitution or restoration inflammatory syndrome [IRIS] [1, 2]. Since 2000, numerous articles have been published on the topic, and the syndrome has been expanded to include patients with a paradoxical reaction while being treated for infections after the withdrawal of immunosuppressive therapy for solid organ transplantation or autoimmune diseases. Moreover, some investigators have applied the term IRIS to include the paradoxical reaction of some infections without prior known immunosuppression, not due to drug reaction, or failure of antimicrobial therapy from resistance or secondary to superinfection. In this chapter, a proposed classification is provided to distinguish the three major but similar conditions: HIV–IRIS, immunosuppressive-IRIS, and paradoxical reaction syndrome [PRS] in apparently normal hosts.

2.2 Paradoxical Reaction Syndrome [PRS]

Paradoxical reactions after the institution of therapy for various infectious agents, not related to failure of therapy from resistance or drug reactions, have been recognized for many years before the AIDS pandemic. The Jarisch–Herxheimer reaction [JHR] was described over a century ago but the pathophysiological mechanisms still remain unclear [3]. JHR was initially described during treatment of early and late syphilis, associated with a transient immunological phenomenon with short-term

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constitutional symptoms such as fever, chills, headaches, myalgia, exacerbation of existing cutaneous lesions, and rarely worsening of central nervous system [CNS] symptoms and signs in some patients with neurosyphilis. This reaction was seen less often with the treatment of borreliosis, brucellosis, typhoid fever, and trichinosis [4]. The PRS was previously attributed to the release of lipopolysaccharide [LPS] or other microbial antigens with a hyperimmune inflammatory reaction. Corticosteroids have been used to treat these PRSs for many years with prompt response but there is a lack of randomized controlled therapeutic trials.

Another PRS that has been well recognized for many years, before the discovery of AIDS, is leprosy reactions that are seen most commonly during or after treatment. Patients with multi-bacillary leprosy are at risk and it is usually not seen with tuberculoid leprosy where the bacterial load is very low. There are two types of paradoxical reactions: reversal reaction [lepra type 1 reaction] which is a delayed hypersensitivity reaction; and erythema nodosum leprosum [lepra type 2 reaction] which is an immune complex reaction [5]. The reversal reaction results from an increase in the Th1 cellular immune response with strong host immune response against *Mycobacterium leprae* in the skin and nerves, with local production of interferon gamma [IFN-¥], tumor necrosis factor [TNF], and cytolytic CD4 T cells [6]. There is also evidence that the Th17 cells participate in the inflammatory response with reduced regulation of T cells; and dysregulation of the metabolic pathways leads to excessive proinflammatory lipid mediators [7]. Clinically, this is manifested with increased erythema, warmth, edema, occasionally ulceration of existing plaque and nodules, associated with painful swollen nerves and symptoms of neuritis [5]. The type 1 reaction is most commonly seen with borderline leprosy or after pregnancy/delivery and can appear up to 2 years after treatment. The lepra type 2 reaction pathogenesis is not completely clear but is believed to result from antigen–antibody mediated immune complex deposition in the skin with subsequent complement activation [5, 6]. Most commonly this involves subcutaneous nodules in clusters but can involve many organs with the presentation of arthralgia or arthritis, dactylitis, severe neuritis, eye disease, lymphadenitis, nasal involvement, nephritis, orchitis, and edema of the face and extremities [5]. It is common to have constitutional symptoms with fever up to 40 °C and rarely is life-threatening with sepsis-like picture. This reaction is most commonly seen in lepromatous and borderline lepromatous leprosy and typically occurs during the first 2 years after initiating therapy, with single or multiple relapsing episodes. A chronic form in 62.5% of cases is seen in Indian cohort [5], which suggests a genetic predisposition. A distinct reaction from the type 1 and type 2 PRS is rarely seen, most commonly in Latin America [mainly Costa Rica and Mexico], with diffuse lepromatous leprosy called Lucio's phenomenon or erythema necroticans [5]. This reaction results in multiple areas of obstructive necrotizing vasculitis with violaceous or hemorrhagic or ulcerative plaques with constitutional symptoms and leukocytosis. Hepatosplenomegaly and lymphadenopathy may be associated with Lucio's phenomenon and urgent treatment with high-dose steroid should be instituted as fatality can occur. Biopsy of lesions shows fibrinoid necrosis of small blood vessels with aggregates of acid-fast bacilli in endothelial cells and large accumulation of macrophages with high levels of angiotensin-converting

enzyme and lysozyme [6]. Lepra type 1 is treated with prednisone [1 mg/kg] with slow tapering and clofazimine can be added for more protracted course. Type 2 lepra reactions can also be treated with prednisone but severe refractory lesions may respond to thalidomide 100 mg four times daily then gradual taper.

Another PRS seen in tropical and subtropical countries is the post-Kala-Azar dermal leishmaniasis [PKDL] and the pathogenesis is unclear. PKDL follows the treatment of visceral leishmaniasis caused by *Leishmania donovani* in 5–10% within 2–4 years after treatment in India and up to 50% of cases within 0–6 months in Sudan [8]. It is more commonly seen after treatment with pentavalent antimony compound. Chronic skin lesions can be present for a few months to a year in Sudan or up to 20 years in India. The skin lesions vary from hyper- or hypopigmented macules, papules, nodules, or verrucous forms with lesions on the face, trunk, extremities, oral mucosa, and genitals. Amastigotes can be detected on skin biopsy in 80% of patients in Sudan. Antileishmanial therapy is usually required in the Indian PKDL but spontaneous resolution can occur in Sudan form although severe cases require treatment [8]. PKDL is a typical example of PRS with immune restoration, a new disease entity that follows visceral leishmaniasis successful therapy and immune recovery, with anti-inflammatory cytokine patterns that are superceded by treatment-induced proinflammatory cytokines, granuloma formation, and healing of lesions [9]. Recently, PKDL was described as HIV-IRIS in patients on ART.

The Mazzotti reaction [previously described in the pre-AIDS era] was considered an adverse event to treatment but is likely a paradoxical reaction to killed microbes. It is a reaction during treatment with diethylcarbamazine for onchocerciasis, consisting of intense pruritic rash sometimes accompanied by fever, malaise, lymphadenopathy, arthralgia, tachycardia, hypotension, and eosinophilia [4]. Blindness can occur with numerous microfilariae in the eyes. The Mazzotti reaction may no longer occur, as the current treatment with ivermectin and doxycycline, is not associated with a similar reaction. Treatment of loiasis in patients with high levels of microfilariae [>2500/mL] may produce a similar paradoxical reaction with diethylcarbamazine, as there is a significant risk of renal and CNS complications [encephalopathy] to the rapid destruction of a large number of microfilariae [10]. A milder reverse reaction can occur in patients with low microfilariae, such as "Calabar" swelling, pruritus, and precipitation of eye involvement. Treatment of the reactions consists of antihistamine and corticosteroids.

Since the description of HIV-IRIS after starting ART in patients, with overt or subclinical opportunistic infections, there have been several reports and studies of PRS occurring in non-HIV patients with various infections and without prior immunosuppression. Paradoxical deterioration or reaction during antituberculosis therapy in apparently normal hosts is the most frequently reported. In 2002, a total of 122 episodes were reviewed with 101 [82.8%] associated with extrapulmonary tuberculosis [TB] [11]. The median time to onset of CNS manifestations [63 days] was longer than the time to onset of manifestation at other sites. The appearance of new lesions in anatomical sites other than the initial presentation was reported in 25.4% of episodes and 95% of the *M. tuberculosis isolates* were susceptible to first-line drugs. Treatment of the paradoxical reactions included steroids [39.3%] and surgical

intervention [60.7%]. In a cohort of 104 patients with confirmed TB, paradoxical deterioration occurred in 15.4% and risk factors included extrapulmonary involvement and lower baseline lymphocyte count with surge during treatment [12]. Paradoxical worsening of TB lymphadenitis appears to be the most frequent reaction, occurring in about 18–25% of treated normal hosts [with repeat negative cultures] [13–15]. Most of these cases occurred early during treatment [69%] but 31% occurred later, a median of 12 months [14]. Paradoxical reaction to antituberculosis therapy has also been reported in children with mainly pulmonary involvement in 9.8% [16]. The most common PRS in children was worsening of preexistent pulmonary lesions [75%] and was greater with younger age and absence of bacille Calmette–Guerin [BCG] vaccination [17].

The rate of paradoxical reaction in immunocompetent patients on anti-TB therapy varies widely, and this may be due to reporting bias in retrospective case series, case definition, or innate differences in different populations. In a prospective study in Africa, 253 patients were treated for pulmonary or extrapulmonary TB with or without HIV infection, the paradoxical reaction occurred in only 1 out of 86 HIV-uninfected patients [1.2%] and IRIS occurred in 21 of 167 [13%] HIV-infected persons [18]. Also in Britain, in a large case control study of 1817 TB patients PRS occurred in 64 of 1692 [3.8%] of HIV-uninfected subjects and IRIS occurred in 18 of 125 [14.4%] HIV-infected persons [19]. In multivariate analysis, the risks of paradoxical reaction were HIV infection [five times the odds], TB lymphadenitis [60-fold], and positive culture [>sixfold] but diabetes significantly reduced the odds.

The first reports of TB-PRS were seen with treatment of CNS TB in non-HIV patients with tuberculomas in 1974 [20] and meningitis in 1980 [21], with the development of new tuberculomas on treatment and basal arachnoiditis. A review of PRS in 156 [HIV-uninfected] patients with TB meningitis has been reported after initial improvement on anti-TB therapy [22]. A number of different adverse events were listed as paradoxical reactions such as expansion of preexisting tuberculoma, or development of new lesions, and clinical worsening with paradoxical cerebrospinal changes. However, other events are well-recognized complications from the meningeal inflammation that probably should not be considered as PRS. These include hydrocephalus, vasculitis with cerebral infarction, radiculomyelitis, syringomyelia, and myelitis. The pathogenesis of PRS-TB is unclear but it is postulated to be related to an exaggerated immune response to the organism antigens in patients on effective anti-TB therapy, rather than uncontrolled mycobacterial replication [22].

Another mycobacterial infection, seen in tropical countries in mainly Central Africa but less often in Southeast Asia, Australia, Central and South America, is Buruli ulcer caused by *Mycobacteria ulcerans.* During the last decade, the paradoxical reaction has been recognized in immunocompetent persons treated with standard 8 weeks of therapy. Paradoxical clinical worsening during treatment with larger lesions especially with trunk localization has been reported in 22% of patients and is associated with a genetic predisposition—polymorphism in the SLC11A1 gene [23]. This gene was previously associated with increased susceptibility to developing Buruli ulcer. In another larger study of 151 patients with Buruli ulcer, peaked paradoxical reaction occurred at 8 weeks after initiation of treatment with

new or progressive ulceration being very common before healing and should not be misinterpreted as a failure of therapy [24].

Whipple disease is a rare condition caused by *Tropheryma whipplei* that can be effectively treated with antibiotics, but occasionally inflammation reappears or worsen after initial improvement with treatment, which was interpreted as refractory or recurrent disease. However, in some cases, no bacteria can be detected by PCR and the reinflammation respond to steroids rather than repeat courses of antimicrobials. In a study cohort of 142 patients, immune reconstitution or paradoxical reaction occurred in 15 [10.5%] of treated patients [25]. The symptoms of the PRS included fever, pleurisy, erythema nodosum, inflammatory orbitopathy, small bowel perforation, and hypothalamic disorder. The complications were mild to severe, with two patients dying, and most patients responded to steroids. Previous immunosuppression was a risk factor for the paradoxical reaction and this was also found in a smaller case series [26]. Further studies of the immunopathology of PRS in Whipple's disease, found that the reaction was mediated by nonspecific activation of CD4+ T cells which was not counterbalanced by regulatory T cells, and was not due to flare-up of pathogen-specific immunoreactivity [27]. In general, the mechanism of PRS for various infections outlined may be related to pathogen-induced immunosuppression reversal with effective antimicrobials and subsequent shift or rebound of the host inflammatory response causing pathological changes. A list of PRS is shown in Table 2.1.

2.3 Immunosuppressive-IRIS

Treatment of pathogens [opportunistic infections] in patients on immunosuppressive agents usually includes withdrawal or dose reduction of these drugs together with antimicrobials, with subsequent immune reconstitution which may lead to worsening of symptoms in some patients from the pathological effect of the host heightened immune response [IRIS]. The two main groups of patients where immunosuppressive-IRIS are well described include organ transplant recipients and persons with autoimmune diseases on immunosuppressive biologics. A similar type of response has also been described in patients recovering from neutropenia and in women during the postpartum period [28], which are not included in this chapter as they do not represent true immunosuppressive-IRIS.

2.3.1 Transplant-IRIS

Transplant-IRIS is an increasingly recognized disease concept associated with a broad range of immunosuppressive therapy-related opportunistic infections, diseases from autoinflammation and drug reactions complicated by viral reactivation [29]. IRIS in these patients have been described with infections such as cryptococcosis,

Table 2.1 Paradoxical reaction syndromes [PRS]: not related to immunosuppression

Pathogen	Type of reaction	Features	Treatment
T. pallidum [syphilis]	Jarish–Herxheimer	Fever, worse rash, incr.	Steroids
[Rarely borreliosis, typhoid etc.]		CNS signs	
M. leprae	Type-1 delayed hypersen	Erythema, incr. rash, neuritis	Steroids, clofaz
[Multi-bacillary]	Type-2 immune complex	EN leprosum	Steroids, thalid
L. donovani	PKDL	Chronic rash, papules/nodules	Anti-leishmania Rx
[Post-visceral leishmanial therapy]			
O. volvulus	Mazzotti reaction	Pruritic rash, fever, adenitis	Steroid
[Post-treatment with diethylcarbamazine for onchocerciasis]			
M. tuberculosis	TB-PRS	Increase adenitis, increase lesions	Steroids
M. ulcerans	Buruli ulcer-PRS	New or progressive ulcers	Continue Rx
T. whippelei	Whipple-PRS	Fever, pleurisy, EN, others	Steroid

clofaz clofazamine, *CNS* central nervous system, *incr* increase, *EN* erythema nodosum, *hypersen* hypersensitivity, *L* leishmania, *M* mycobacteria, *O* onchocerca, *PKDL* post-Kala-Azar dermal leishmaniasis, *Rx* treatment, *T* tropheryma

TB, herpes zoster, herpes simplex, cytomegalovirus, and others; but also noninfectious diseases such as sarcoidosis and drug-induced hypersensitivity syndrome with life-threatening multiorgan dysfunction [29].

The pathogenesis of immunosuppressive-IRIS is not well studied as HIV-IRIS and it is unclear whether or not the mechanisms are similar. A few animal studies have been performed but with a limited number of immunosuppressive agents. In a rabbit model of TB and steroid-induced immunosuppression, the withdrawal of dexamethasone led to lymphoid recovery with some animals developing multicentric large caseous granulomas [30]. The development and severity of IRIS were dependent on the antigen load at the time of immunosuppression and subsequent bacillary replication. In a mouse model of Cryptococcus infection in lymphocyte-deficient RAG-1 animals, 4 weeks after infection purified CD4+ cells were adoptively transferred into the mice [31]. The reconstitution of the CD4+ cells was sufficient to induce severe inflammatory disease similar to clinical IRIS. Multiorgan dysfunction and inflammation were associated with the release of distinct proinflammatory cytokines, interferon gamma [IFN-¥], interleukin [IL]-6, and tumor necrosis factor alpha [TNFα]. However, IFN-¥-mediated effects were not necessary for the induction of IRIS. This model, however, may be more applicable to HIV-related IRIS than immunosuppressive-IRIS.

Immunosuppressive agents in transplant recipients primarily target the Th1 and Th17 cells, which are the primary mediators of allograft rejection, whereas regulatory T cells [Tregs] and Th2 cells [which mainly secrete anti-inflammatory cytokines IL-4 and IL-10] promote graft tolerance [32, 33]. Corticosteroids decrease Th1 and Th17 cells and minimally increase Th2 and Treg cells [34, 35]. The calcineurin inhibitors are potent suppressors of Th1 and Th17 cells and function [tacrolimus more active than cyclosporine A] and promote Th2 cells [36]. Mycophenolate mofetil suppresses Th1, Th17, and Th2 cells, as does rapamycin but the latter promotes Treg [36]. Immunosuppressive-IRIS, in general, is related to the reversal of the anti-inflammatory state [from withdrawal or decrease in immunosuppression] to a proinflammatory response with the institution of antimicrobial therapy, and possibly reversal of pathogen-induced immunosuppression [37].

Cryptococcosis is the most frequently described opportunistic infection of transplant-IRIS, which has been partly attributed to its immunosuppressive effect itself that is reversible with antifungal therapy and the potent mitogenic activity of the cell wall [37, 38]. In solid organ transplant recipients with cryptococcosis, 5–14% may develop IRIS with antifungal therapy which is more prevalent with greater immunosuppression [combination of tacrolimus, mycophenolate mofetil, and prednisone] and disseminated disease [36]. In a study of 89 solid organ transplant recipients with cryptococcosis, 13 [14%] develop IRIS and the primary risk factors were discontinuation of calcineurin inhibitor [fivefold increase] and central nervous system infection [39]. IRIS most commonly occurred 4–6 weeks after initiation of antifungal therapy but can be late as 9 months after [36]. The manifestation of IRIS may include lymphadenitis, cellulitis, aseptic meningitis, worsening cerebral lesions, hydrocephalus, spinal arachnoiditis, and lung nodules. The most appropriate treatment of cryptococosis-IRIS is unclear and the 90-day mortality is not increased in patients with IRIS versus those without IRIS [36]. Other invasive mycoses associated with transplant-IRIS are less commonly reported but include aspergillosis [associated with neutropenia and stem cell transplant], candidiasis, histoplasmosis, and other rare fungal infection [36].

TB complicating organ transplantation is 36–74-fold higher than the general population and the incidence average 1.2–6.4%, but up to 15% in high-risk regions [40]. Th1 and IFN-¥ producing cells are responsible for human resistance against TB, whereas Th2 cells inhibit the immune response to the organism [41]. Similar to cryptococcus, *M. tuberculosis* can impair the immune response by inducing Th2 and Treg cells [42], and antituberculous therapy may reverse the immune suppression and lead to the severe inflammatory reaction. This is believed to be the mechanism in PRS during TB treatment of normal hosts and may also play a role in TB-IRIS associated with immunosuppression or HIV. In a study of 64 consecutive organ transplant recipients with TB followed for 12 months, IRIS developed in 14% at a median of 47 days after onset of anti-TB therapy [43]. However, the data are insufficient to determine whether or not the frequency of transplant TB-IRIS is any greater than TB-PRS reported in apparently normal subjects. The manifestations of transplant TB-IRIS are similar to TB-PRS, such as new-onset or worsening pleural effusion, worsening pulmonary lesions, unexplained fever, new-onset pericardial

effusion, new-onset lymphadenopathy, worsening or new brain tuberculoma, and hydrocephalus, in the absence of drug resistance or failure to suppress the growth of the mycobacteria [43]. The risk of IRIS was associated with liver transplantation, cytomegalovirus infection, and rifampin use.

Virus-related IRIS in transplant recipients is infrequently reported despite the frequency of reactivation of the herpes group of viruses and diseases caused by these pathogens. Cytomegalovirus [CMV] is a significant and important cause of morbidity and mortality in transplant recipients, with a wide spectrum of organ involvement but only a few cases of CMV-IRIS reported. CMV-IRIS in transplant recipients has been attributed to profound Th17 cell depletion and weak ant-CMV CD4+ T cell response but no impairment of Tregs [44]. CMV-IRIS in transplant recipients is manifested mainly as worsening chorioretinitis, which is rare in these patients unlike people with AIDs where it is one of the commonest manifestations of CMV disease. In a report of 18 HIV-negative immunosuppressed patients with CMV retinitis [10 transplant recipients], IRIS occurred in 13% per person-year [45]. BK virus [a polyoma virus] occasionally causes nephropathy in renal transplantation and worsening renal function after reduction of immunosuppressive drugs has been attributed to IRIS [46]. Allograft biopsy showed massive lymphocytic infiltration with the emergence of specific antibodies and T cells.

The optimal management of transplant-IRIS is not well defined but has included corticosteroids, non-steroidal anti-inflammatory drugs, intravenous IgG, and surgery [vitrectomy] [36]. Complete withdrawal of immunosuppressive agents should be avoided in opportunistic infections and tapering of these drugs may reduce the risk of IRIS.

2.3.2 Biologic Therapy-IRIS

Since the late 1990s, there has been a proliferation of biologics introduced for the treatment of autoimmune disorders, cancers, and idiopathic inflammatory conditions that revolutionized medical care in these areas. However, treatment with these biologics carries the risk of opportunistic infections and subsequent drug withdrawal may result in serious IRIS. The major biologics in clinical use are humanized monoclonal antibodies or small molecule kinase inhibitors that work in one of three ways: interfere with cytokine function or production; inhibit the "second signal" required for T cell activation; and deplete B cells [47].

Natalizumab is a humanized monoclonal IgG4k antibody that binds the α4 subunit of the integrin α4/β1 heterodimer expressed by lymphocytes and may act by preventing migration of lymphocytes from the bloodstream across the blood-brain barrier [48]. It also affects T cell receptor performance [49] and is used to treat multiple sclerosis [MS] and Crohn's disease. One of the major complications of natalizumab therapy in MS is the development of progressive multifocal leukoencephalopathy [PML] caused by the reactivation of John Cunningham polyomavirus [JCV]. Once PML is diagnosed, the drug is discontinued or removed by

plasma exchange [PLEX] or immunoadsorption [IA] as it can remain active for up to 3 months [50]. PML-IRIS is commonly reported after discontinuation of natalizumab [23 of 40 cases] manifested by worsening neurological deficits and inflammatory changes on neuroimaging, contrast enhancement of PML lesions was found in 17 of 42 cases before the withdrawal of the biologic [51]. Corticosteroid therapy was associated with a better outcome in this report. In a recent review, it was concluded that nearly all patients with PML develop IRIS after natalizumab withdrawal [52]. Unmasking of subclinical PML can also occur after discontinuation of the biologic for other reasons. PML-IRIS occurs soon after the removal of natalizumab from the body and lymphocytes return to the brain and immunity is restored. JCV-specific CD4+ T cells play an important role in both eliminating the virus but also causing massive inflammation with often fatal outcome in PML-IRIS [53]. Histologically PML is usually characterized by the absence of inflammatory reaction and white matter lesions. However, PML-IRIS is distinguished by marked inflammation with increased CD8+ T cells, macrophages, and plasma cells, with no or low numbers of virally infected cells and limited CD 4+ cells [54]. Corticosteroids have been associated with the best response for natalizumab PML-IRIS, high dose for 3–5 days then taper over 6–8 weeks [52].

Tumor necrosis factor [TNF]-α antagonists are used to treat several autoimmune and inflammatory conditions, such as rheumatoid arthritis [RA], psoriasis and psoriatic arthritis, spondylarthropathies, and inflammatory bowel disease. TNF-α is a key proinflammatory cytokine produced by Th1 lymphocytes that plays an important role in the recruitment of immune cells, macrophage activation, and granuloma formation [55]. It is necessary to induce Th1 cells to maintain granulomas sequestering mycobacteria and control infection [55, 56]. There are currently five TNF-α inhibitors being used for therapeutics and treatment with these agents have been associated with reactivation of TB, such as adalimumab, infliximab, and etanercept [52]. Recently, there have been multiple reports of the clinical worsening of TB after starting anti-TB therapy and discontinuation of the TNF-α inhibitors attributed to TB-IRIS [57–62]. The paradoxical worsening may occur in 5–20 weeks after initial improvement, with fever, malaise, bulky lymphadenopathy, and new pulmonary infiltrates [52]. The occurrence of IRIS after cessation of TNF-α inhibitor is longer for infliximab [dosed every 8 weeks] than for adalimumab and etanercept which are cleared more quickly and dosed more frequently [60, 61]. Treatment of TB-IRIS usually involves starting steroids to control the inflammatory response with the continuation of anti-TB therapy and resuming anti-TNF therapy at a lower dose may be helpful.

Paradoxical reactions have also been reported with the treatment of invasive fungal infections after discontinuation of TNF-α antagonists. These include IRIS in 8 of 19 [42%] patients who developed histoplasmosis with clinical deterioration after stopping TNF-α blockade [63]. These patients usually present with severe pneumonia with initial improvement on antifungal therapy and worsening later, even 10 weeks after the last dose of the anti-TNF inhibitor and continuation of antifungal agent. Cryptococcosis appears to be less of a complication of TNF-α inhibitors than with organ transplant immunosuppression and cryptococcal-IRIS has been rarely

reported, with worsening lung infiltrates after discontinuation of adalimumab for rheumatoid arthritis [64].

Rituximab is a chimeric IgG1 monoclonal antibody that depletes B cells by targeting CD20 on B cells [47]. It is used to treat lymphoproliferative disorders, MS, immune thrombocytopenic purpura [ITP] and several rheumatic diseases. There is also evidence that it impairs Th17 response and increases the susceptibility to T cell-related infections [65]. Although 76 cases of PML have been reported with the use of rituximab by 2008, IRIS has been rarely reported [52]. TB-IRIS was reported after completion of therapy for lymphoma with a rituximab-containing regimen [66].

Alemtuzumab is an IgG1 monoclonal antibody that depletes B and T cells by targeting CD52 expressed on these cells. It is used to treat B-cell chronic leukemia and MS [Canada and Europe]. Opportunistic infections include PML and cryptococcosis but infection-IRIS is rarely reported, case of cryptococcosis [67]. For unclear reasons, this biologic is more commonly associated with autoimmune-IRIS. During clinical trials of treatment of MS, alemtuzumab was associated with an increased incidence of antibody-mediated autoimmune disorders of up to 20%, with Grave's disease being the most common [52]. Other noninfectious IRIS included ITP, sarcoidosis, and glomerulopathy.

IRIS can also present with drug-induced hypersensitivity syndrome with high fever, severe skin rash, frequent relapse, and development of severe organ failure, despite the withdrawal of the causative drug [68]. Table 2.2 summarizes IRIS seen with immunosuppression with organ transplantation and biologics. Conversely, immune checkpoint inhibitors, pembrolizumab or nivolumab, used to reinvigorate anti-tumor cell activity directed in a variety of cancers have recently been shown in small observational studies to be beneficial in the treatment of PML [69, 70]. These agents appear to work by blocking programmed cell death protein-1 [PD-1] to increase JC virus-specific CD8+ T cells.

Table 2.2 Immunosuppressive-IRIS

(a) Transplant-IRIS
Infections: Cryptococcosis [most common IRIS], TB, herpes zoster, herpes simplex, cytomegalovirus, BK virus, etc.
Auto-inflammation: Sarcoidosis, thyroiditis, Graves' disease
Severe drug hypersensitivity reactions
(b) Biologic therapy-IRIS
Natalizumab—impairs T cell function; most commonly associated with PML-IRIS
TNF-α antagonists [infliximab, adalimumab, etanercept]—most commonly associated with TB-IRIS, rarely CM-IRIS
Rituximab, depletes B-cells—rarely associated with PML- and TB-IRIS
Altemtuzumab—depletes B & T lymphocytes; rarely associated IRIS [CM, PML], most commonly associated with autoimmune-IRIS [Graves' disease, ITP, sarcoidosis]

CM cryptococcal meningitis, *MS* multiple sclerosis, *PML* multifocal leukoencephalopathy, *TB* tuberculosis

2.4 HIV-IRIS

The depletion of the CD4+ T cells is the primary factor leading to severe immune deficiency in people with AIDS and predisposition to a wide variety of opportunistic infections. However, since the advent of highly active ART, improvement of CD4 cell count and decline in HIV viral load have been associated with paradoxical worsening of opportunistic infection in some patients [at the original site or new site], or the unmasking of occult, subclinical infections soon after institution of ART. The incidence of IRIS ranges from 10% to 23% of all persons starting ART and from 8% to 43% in those with existing opportunistic infections [71]. However, there is no validated case definition or universally accepted criteria. French et al. [2] diagnostic criteria in 2000 was based on two major and three minor criteria; including atypical worsening of opportunistic infection or tumor while showing therapeutic response to ART [>1 log decline in viral load] or two minor criteria [increase in CD4 cell count, resolution of symptoms, or pathogen-specific immune response]. The AIDS Clinical Trials Group adapted a definition proposed by Shelbourne et al. in 2002 [72], which included new onset of worsening of symptoms of an infection or inflammation after starting ART; symptoms not explained by newly acquired infection or expected course of previous infection, or due to adverse drug reaction; and decrease in viral load >1 $\log_{10}$ copies/mL. However, after comparing the two case definitions and evaluation of expert opinions on a prospective cohort of 495 adults starting ART in South Africa, Haddow et al. [71] proposed a revised definition for both paradoxical and unmasking IRIS. To complicate the issue of definition further, an International Network for the Study of HIV proposed their definition of HIV TB-IRIS [73].

2.4.1 Pathogenesis of HIV-IRIS

The pathogenesis HIV-IRIS is incompletely understood and there is no universal agreement on the mechanisms. Moreover, it is unclear whether the mechanisms of IRIS associated with HIV infection are similar to immunosuppressive-IRIS. IRIS, in general, is characterized by an intense inflammatory reaction to dead or latent organisms or sometimes to self-antigens with heightened but dysregulated immune response, associated with tissue destruction and clinical disease. It has been proposed that IRIS is caused by a dysregulation of the expanding population of CD4+ T cells specific for a coinfecting opportunistic pathogen. However, others disagree and propose that the mechanisms are shared irrespective of the pathogen. Insights of the pathogenesis of HIV-IRIS may be gleamed from review of animal models, clinical experience, and human studies on the immune response.

Risk factors for HIV-IRIS have been defined in multiple clinical studies and there is a strong association of severe depletion of CD4+ T cell count and development of IRIS, the most severely lymphocytopenia patients [CD4 cell count <50

cells/mL] being at the greatest risk [74–77]. The presence of an opportunistic infection close to the time of starting ART greatly increases the risk of IRIS [75, 76]. Although HIV-IRIS has been associated with a wide array of pathogens and tumors, it is most commonly reported with CMV retinitis [37.7%], cryptococcal meningitis [19.5%], TB [15.7%], and PML [16.7%] [77].

Murine models of T cell depleted animals have been used to study the mechanisms of IRIS associated with *Pneumocystis carinii, Mycobacterium avium*, and *C. neoformans* [31, 78, 79]. Reconstitution of CD4+ T cells is sufficient to drive the inflammatory response in IRIS. Multiorgan inflammation is associated with the systemic release of proinflammatory cytokines, IFN-¥, IL-6, and TNF-α [31]. IRIS development requires antigen recognition by T cells and antigen-driven CD4+ T cell responses [31, 79]. But disease is associated with impaired, rather than augmented, T cell expansion and function and not dependent on lymphopenia-induced T cell proliferation [79]. In a *M. avium*-infected T cell depleted mice, fatal inflammatory disease occurred with reconstitution with CD4+ T cells but IL-6 neutralization extends survival and alleviates wasting disease; and combined blockade of IL-6 and IFN-¥ reduces further IRIS pathology after the onset of wasting disease [80],indicating a role of IL-6 and IFN-¥ in the pathogenesis of IRIS.

Human studies of HIV-IRIS also support the results of animal experiments. In prospective studies of TB/ HIV-infected patients just starting ART, IRIS was preceded by CD4+ T cell activation with rapid expansion of TB-specific polyfunctional T cell responses and increased inflammatory cytokines and chemokines [IL-6, TNF-α, IFN-¥-induced protein, and IL-7] by week 4 in patients with IRIS [81, 82]. In a study of TB meningitis HIV-IRIS, neutrophils and their mediators were also closely related to CNS inflammation of IRIS and high baseline TB antigen load was a greater predictor of paradoxical reaction [83]. Others have also implicated the granule exocytosis pathway in TB-IRIS pathophysiology [84]. HIV-associated TB-IRIS is also characterized by Toll-like receptor signaling and TREM-1 activation of the inflammasome [85]. More recent studies have confirmed that TB-meningitis-IRIS is characterized by neutrophil and inflammasome-mediated inflammatory responses, highly compartmentalized to the brain; and early neutrophil-activation could be detected before anti-TB treatment and IRIS, which could be used to predict patients at risk for CNS TB-IRIS [86]. In cryptococcal meningitis high plasma IL-5 and IL-7 levels pre-ART were associated with increased risk of developing IRIS, which may suggest a role of Th2 environment with impaired clearance of cryptococci and pathway dysfunction in T cells [87]. Recent data from MAC-IRIS patients also noted the restoration of monocyte responses with the expansion of polyfunctional MAC-specific T-bet^{low} CD4+ cells and exuberant production of cytokines that overwhelms the regulatory and inhibitory mechanisms [88].

Based on cumulative evidence of animal experiments and human studies, investigators from the National Institute of Health [NIH] propose a common mechanism for HIV and immunosuppressive-IRIS: that IRIS is the product of exaggerated response of the innate immune system to T cell help following the reversal of various forms of immunosuppression in pathogen-infected hosts [89]. This mechanism can explain the variety of manifestations of IRIS.

2.5 Clinical Types of HIV-IRIS

The clinical subtypes of HIV-IRIS are largely classified according to the opportunistic pathogens, see Table 2.3, but sometimes it is categorized based on the specific organ involved, such as neurologic or CNS-IRIS.

2.5.1 HIV TB-IRIS

HIV-related TB-IRIS is most frequently seen where HIV-1 coinfection among TB cases is the highest—in Africa which accounts for 78% of the total HIV-TB coinfected cases [90]. In 2013, there were an estimated 9.0 million cases of active TB and 1.1 million [13%] were HIV coinfected [91]. HIV infection increases the risk for active TB by 26–31-fold greater than noninfected people and the course is more rapid with poorer survival even when controlling for the CD4+ T cells counts [92]. Active TB is immunosuppressive itself and can cause lymphocytopenia in the absence of HIV or immunosuppression. HIV infects and depletes CD4+ T

Table 2.3 HIV-IRIS subtypes

Pathogens	Terminology	Features
M. tuberculosis	TB-IRIS [≅18%]	Mainly paradoxical worsening adenitis, ↑ lesions, CNS signs, etc.
C. neoformans	CM-IRIS [13–20%] 20% of CM unmasked	Worsening meningitis, adenitis, CNS mass, lung, eye, skin lesions, etc.
JC virus	PML-IRIS [≅30%]	↑ Lesions, enhanced MRI, ↑ outcome
Cytomegalovirus	CMV-IRIS [up to 70%]	>60% unmasked, ↑ retinitis, uveitis
Human herpes virus-8	KS-IRIS [≅14%] Risk greater in Africa	↑ Lesions, ulcerations, edema, viscera
MAC	MAC-IRIS [unmasked or paradoxical reaction]	↑ Adenitis, abscesses, involve organs
PJP	PJP-IRIS [4–5%]	Paradoxical worsening of infiltrates
Bacille Calmette Guerin	BCG-IRIS [≅8%]	Necrotizing lymphadenitis
Varicella zoster virus	VZV-IRIS [common with unmasking]	Dermatome, multi dermatomes, rare myelitis
Epstein-Bar virus	Lymphoma-IRIS	Unmasking with ↑ lymph nodes, fever
HBV/HCV	HBV OR HCV-IRIS	Greater for HBV, hepatitis flare, ↑ ALT
HSV, MCV, HPV	Mucocutaneous-IRIS	Common unmasking: ulcers, warts, etc.
HIV	HIV-neuro-IRIS [rare] Unmasked months to years	Worsening cognition, focal signs, T cell encephalitis
Drugs	Hypersensitivity reaction	Rash, fever, possible eosinophilia

HBV hepatitis B virus, *HCV* hepatitis C virus, HSV herpes simplex virus, *MAC* mycobacteria avium complex, *HPV* human papilloma virus, *MCV* molluscum contagiosum virus, *NHL* non-Hodgkin lymphoma, *PJP* pneumocystis jirovecii pneumoniae

cells, including those that are *M. tuberculosis*-specific, resulting in decreased cytokines [TNF-α, IFN-¥, and others] that are important for the control of both pathogens. There is evidence from a study in Asia that HIV-associated TB-IRIS is related to polymorphisms in immune-related genes, but none were common across ethnicities [93].

In a recent review and meta-analysis of 40 studies, the incidence of IRIS was about 18% among patients with HIV-associated TB and the attributable mortality of TB-IRIS was about 2% [94]. However, patients with TB meningitis are at higher risk of developing IRIS [31–47%] and with a mortality of up to 30% after developing IRIS [90, 95]. Although, a prospective study of 806 participants with HIV-TB coinfection reported that CNS TB-IRIS was uncommon [6.6%] [96]. Besides low CD4+ T cell counts [<50 cells/μL], a risk factor for TB-IRIS has been shown by randomized studies to be associated with the initiation of ART soon after starting antituberculous therapy [96–98]. However, the benefits of starting early ART in reducing mortality and opportunistic infections outweigh the risk of TB-IRIS in subjects with very low CD4+ T cell count [<50 to 100 cells/μL] [89]. In tuberculous meningitis, however, immediate ART did not improve mortality and was associated with excess grade four adverse events [99]. Hence, in HIV-associated TB meningitis ART should be delayed for at least 2 weeks or more after initiation of antituberculous therapy. Patients with CD4+ T cell counts >50 to 100 cells/μL could be started on ART 2–12 weeks after. High HIV viral load and extrapulmonary and disseminated TB [likely related to high bacterial burden] are other risk factors for TB-IRIS [90, 99]. The manifestation of HIV-related TB-IRIS is similar to the clinical presentation of TB-PRS seen in patients without underlying disease or immunosuppression; such as recurrent, prolonged fever, increased or suppurative lymphadenitis, worsening pulmonary lesions or pleural effusions and increased intracranial lesions and complications. In most cases, TB-IRIS occurs in patients with diagnosed TB with initial improvement on treatment and flare-up of symptoms a median of 2 weeks after starting ART. Less commonly is unmasking TB-IRIS in previously undiagnosed and untreated TB, presenting after initiation of ART with marked inflammatory features of active *M. tuberculosis* infection [73]. To make a diagnosis of TB-IRIS, it is important to exclude drug-resistant *M. tuberculosis,* the presence of other opportunistic infection, poor drug adherence, and adverse drug reactions. Although most studies and case reports have involved adults, HIV-TB-IRIS is also reported less commonly in children. In a review of 303 cases of TB-IRIS in children, most cases presented as unmasking TB-IRIS, 270 or 89% [100].

In a recent RCT of 240 subjects, prednisone during the first 4 weeks after the initiation of ART in HIV-infected patients with active TB lowered the risk of IRIS compared to placebo without increasing the risk of severe infections [101]. The absolute decrease in TB-IRIS was 14.2% with a relative risk reduction of 30%, mainly of lymph node involvement or abscess formation and new or worsening features on radiography. Open-labeled prednisone was used to treat IRIS in 28.3% in the placebo group and 13.3% in the treated group [101]. This trial does not provide a strong argument for prophylactic prednisone as >70% of untreated patients will not require treatment for IRIS.

2.5.2 HIV-Associated Cryptococcal-IRIS

Cryptococcal meningitis [CM] is common worldwide in patients with advanced AIDS and the majority of infected patients have CD4+ T cell count <100 cells/μL. CM is the most common cause of meningitis in HIV-adults in sub-Saharan Africa and accounts for about 20–25% AIDS-related deaths [102]. In a prospective observational study of 501 HIV-CM patients from Africa and Asia, 13% developed CM-IRIS which was associated with high cerebrospinal fluid [CSF] fungal burden but not with the time of initiation on ART [103]. A small prospective, randomized study in one center in Africa previously reported higher mortality with earlier ART [within 72 h of CM diagnosis] compared to delayed ART [after 10 weeks of fluconazole alone] [104]. The cause for the increased early mortality was unclear but postulated to be secondary to CM-IRIS. This observation was confirmed from a larger study [177 participants] from Uganda and South Africa with HIV related CM. Earlier ART [1–2 weeks after CM diagnosis] was associated with a mortality of 45%, compared to delayed ART [5 weeks after initiation of amphotericin B and fluconazole] with a mortality of 30%, $p = 0.03$ [105]. Few CSF leucocytes [<5 cells/mL^3] were especially strongly associated with excess mortality from earlier ART. CM-IRIS was higher [20%] with earlier ART than delayed ART [13%] but not statistically significant, possibly from being underpowered. However, it was unclear whether the excess deaths in the earlier ART group were directly due to sequelae of CM or due to IRIS.

Most cases of paradoxical CM occur in 1–2 months post-ART initiation with worsening aseptic meningitis and increased CSF inflammatory changes compared to baseline at diagnosis of meningitis; and other manifestations such as cryptococomas, lymphadenitis, pneumonitis, skin, soft tissue, bone and joint lesions, and chorioretinitis [105]. In sub-Saharan Africa, 20–33% of all cases of CM occur after initiation of ART in the first 2 months, presumably unmasking CM-IRIS [106]. These cases of CM unmasked by ART initiation likely represent early subclinical infection with the fungus, as screening of blood for cryptococcal antigenemia is highly effective in identifying patients at risk of developing CM on ART [107]. Although the acute mortality of CM is similar between patients developing infection before and after starting ART, the 1-year survival of those on ART at presentation was much better [108]. The recognized risk factors for CM-IRIS in HIV include high fungal burden in CSF, lack of CSF inflammation, and extremely low CD4 cell count with poor recovery after ART, and low antibody response to cryptococcal antigens also appears to be a predictor of the reaction [109].

HIV-Associated PML-IRIS

Before the advent of highly active ART, PML was a uniformly fatal disease in AIDS patients, usually within 6 months after diagnosis. The incidence of PML has dramatically been reduced with early institution of ART before AIDS complications. Almost one-third of patients with PML develop IRIS after initiating ART and survival appears to be higher in those with PML-IRIS compared to patients without IRIS [110]. Patients who developed PML-IRIS had lower baseline CD4+ T cell

count and a greater decline in HIV-RNA levels in response to ART. Gadolinium enhancement on MRI was found in 30.5% of patients with PML-IRIS cases versus 2.5% in PML without IRIS. This inflammatory reaction had previously been correlated with CD8+ T cells in the brain lesions and control of the JCV infection [111].

2.5.3 HIV CNS-IRIS Without Opportunistic Infection

IRIS affecting the brain is commonly seen in patients with AIDS initiating ART in the presence of CNS opportunistic infection, usually from weeks to months after starting therapy for HIV. The acute fulminant form is the result of enhanced immune response targeting the opportunistic microbial agent, and the brain suffering collateral damage. Despite adequate control of HIV replication in the brain, some patients develop a chronic form of T cell encephalitis which appears to be driven by continued production of HIV-Tat protein [112]. The incubation period of this rare entity varies from 1 month to over 2 years, coinciding with increased CD4+ T cell counts [113, 114]. Patients may present with chronic or subacute encephalopathy/encephalitis, demyelinating lesions, headaches, impaired speech or hearing, weakness, disorientation, and ataxia [115]. Pathology of brain biopsy showed robust CD8+ lymphocyte infiltration in the parenchyma and perivascular region, reactive astrocytosis and microglial activation; and a subset of patients may show axonal damage and myelin loss [113]. On rare occasions acute severe neurological impairment has been reported within 3 months of starting ART with rapid immune recovery and response to corticosteroids; and also 10 years after starting ART with relapsing neurological complications after response to corticosteroids, with brain biopsy confirming CD8+ T cell encephalitis [115].

2.5.4 HIV CMV-IRIS

CMV diseases, especially retinitis, were once common complications of AIDS but in recent times with earlier treatment with ART have become rare complications. In a single institution experience from 2003 to 2012, 116 patients with HIV-related CMV retinitis on ART initiation or during the subsequent 6 months were reviewed for analysis [116]. Of the 75 patients included in the analysis, CMV-IRIS developed in 55 patients [73.3%], 35 after starting ART [unmasking CMV-IRIS] and 20 experienced paradoxical clinical worsening of retinitis [paradoxical CMV-IRIS]. Most cases of CMV-IRIS developed within 3 months of starting ART with clinical evidence of worsening vision from retinitis. Six patients with CMV-IRIS later developed immune recovery uveitis. In this study, steroids were considered contraindicated because of active CMV infection.

HIV Kaposi Sarcoma-IRIS

Kaposi sarcoma [KS] is caused by the human herpes type-8 or Kaposi sarcoma herpes virus [KSHV], which is also responsible for primary lymphoma effusion and

a form of multicentric Castleman disease [117–119]. As with other AIDS-defining diseases, there has been a marked decrease in the incidence of KS in the past 10–15 years directly related to earlier treatment of HIV infection. Analysis of a large cohort of HIV-infected patients [$N = 66,369$] in 2013 indicated that there were 1.6 additional KS cases per 1000 person-years during the first 3 months of ART; suggesting that IRIS may contribute to the risk of KS appearance on treatment [120]. In another study around the same period, a pooled analysis of three prospective cohorts of ART-naïve HIV-infected patients with KS from sub-Saharan Africa and one from the UK was performed for the incidence of KS-IRIS [121]. Fifty-eight of 417 [13.9%] patients developed KS-IRIS with an incidence of 2.5 times higher in African versus European cohorts [$p = 001$]. Moreover, the mortality from KS was 3.3-fold higher in African patients. This difference was related to more advanced KS and lower chemotherapy availability in Africa. Advanced KS stage and high plasma HIV1 RNA load were predictors of IRIS, as well as detectable KSHV plasma DNA at baseline. A recent study has also reported that the use of corticosteroids [for management of pneumocystis pneumonia] increases the risk of KS-IRIS [37%] and KS-associated mortality [122].

Recently, investigators at NIH characterized and defined a new syndrome called KSHV-inflammatory cytokine syndrome [KICS], which has some features of IRIS but not categorized as KS-IRIS [123]. Of the 10 patients described in the report, all had HIV infection and 8 were on ART with suppressed HIV viral load <50 copies/mL in five subjects. All patients had multiple symptoms including gastrointestinal disturbance, edema, respiratory symptoms, and effusions, with evidence of elevated C-reactive protein, Il-6, and IL-10. Mortality was high, as 6 died with a median survival of 13.6 months. Laboratory abnormalities included anemia, hypoalbuminemia and thrombocytopenia, high KSHV viral load in plasma [>1000 copies/mL] and imaging evidence of lymphadenopathy, splenomegaly, and hepatomegaly. Currently it is unclear whether KICS is a severe form of KS-IRIS, as some patients were not on ART, but there may be some overlap [personal communication with Robert Yoachoan of NIH].

Miscellaneous HIV-IRIS

Multiple infections complicating HIV/AIDS and malignancy, other than KS, can present with IRIS; see Table 2.3 for a list of HIV-IRIS subtypes. A large prospective cohort study from the USA of 2610 HIV-infected subjects initiating ART during 1996–2007 were assessed for IRIS between 7 and 180 days after starting therapy [124]. IRIS occurred in 10.6% of patients with oral-mucosal [including esophageal and vaginal] candidiasis being the commonest manifestation. Paradoxical worsening of preexisting opportunistic infections was not evaluated and new appearance of mucosal candidiasis just after 1 week of ART was listed as IRIS, when these conditions may still be related to HIV-immunosuppression before immune restoration. Furthermore, including the appearance of vaginal candidiasis as an IRIS event is very questionable, as this condition occurs very frequently in normal hosts at any time and could be coincidental after starting ART. Other IRIS defining diagnosis in this study included CMV, *Mycobacterium avium* complex [MAC], Pneumocystis pneumonia, varicella zoster, KS, non-Hodgkin lymphoma [NHL], and one case of

TB-IRIS. In a smaller prospective study from South Africa of 498 adults initiating ART, 22.9% developed IRIS [36% paradoxical, 64% unmasking] and mucocutaneous conditions accounted for 68% of IRIS events, mainly folliculitis, warts, genital ulcers, and herpes zoster, and TB accounted for 25% of events [125]. Pneumocystis pneumonia has only been reported to be associated with IRIS in 4% of cases [126], and disseminated MAC is now a rare disease. MAC-IRIS most commonly presented with increased lymphadenitis [peripheral, abdominal, or thoracic], abscesses, visceral organs, and lung involvement with a variable course and outcome [127]. Cerebral toxoplasmosis has rarely been reported to present as HIV-IRIS.

Most cancer risk of AIDS [KS and NHL] are explained by the immunodeficiency prior to ART institution, however, an increased cancer risk was previously reported within the first 3 months of therapy, odds ratio 2.31, confidence interval 1.33–4.0 [128]. Rates of NHL among patients with HIV infection are highest within the first 6 months of starting ART, particularly in those with low CD4 counts. Unmasking of lymphoma within weeks of initiating ART is considered "lymphoma-IRIS". In one study of 482 HIV-infected subjects with NHL, 12% were diagnosed with lymphoma-IRIS [129].

Genital ulcer disease [GUD] due to herpes simplex virus [HSV]-2 has also been reported to increase during the first 1–3 months of ART, especially in women with very low CD4+ counts and considered as a form of IRIS. In one study of 3381 HIV/HSV-2-coinfected individuals, GUD incidence increased from 15.0 episodes per 100 person-years before ART to 26.9 episodes per 100 person-years in the first 3 months after ART initiation, $p = 0.03$ [130].

Coinfection of HIV with hepatitis B and hepatitis C is common and these viruses contribute to immune activation, morbidity, and mortality. However, there is some but limited data to suggest that hepatitis C coinfection blunts CD4+ T cell recovery during ART therapy [131]. Hence, hepatitis C-IRIS maybe expected to occur rarely in HIV subjects. However, grade 3–4 hepatotoxicity after ART occurs more frequently in patients coinfected with hepatitis B or C, but this may be multifactorial including IRIS and drug toxicity [132]. Hepatitis C-IRIS may be defined as clinical hepatitis after initiation of ART, associated with a fall in HIV viral load, significant increase in CD4+ and CD8+ T cells, increase in hepatitis C [HCV] RNA and significant increase in alanine aminotransferase [ALT]. Hepatitis flare was defined for HIV-hepatitis B [HBV] individuals in the Thailand [Tenofovir in Co-infection [TICO] study], as ALT over five times the upper limit of normal or over 100 IU/L rise over baseline if abnormal within 3 months of treatment [133]. Transient increase in HCV RNA and rarely HCV clearance has been described after initiation of ART, but clinical hepatitis flare is very uncommon [132]. HBV flare or HBV-IRIS is more commonly reported than HCV-IRIS. Prospective, randomized studies have reported HBV-IRIS in about 26% of coinfected subjects [133, 134]. Risk factors were advanced HIV infection [median CD4+ T cells 36 cells/μL], high baseline HBV DNA, and ALT. HBV-IRIS may be followed by anti-HBVe, and rarely anti-HBs-Ag seroconversion. In the TICO study, 33% lost HBeAg and 8% lost HBsAg [132]. However, in patients with underlying cirrhosis HBV-IRIS can lead to hepatic decompensation and even death [132].

BCG immunization after birth is routinely used in developing countries with moderate to high incidence of TB. The vaccine consists of live attenuated *Mycobacterium bovis* Bacillus Calmette–Guerin and treatment with ART in the neonatal period poses a risk of severe reaction or BCG-IRIS. Severe reactions with BCG in infants soon after starting ART have been reported and the World Health Organization does not recommend BCG vaccination in HIV-infected children [135]. In a prospective study from South Africa, 369 infants were assessed for IRIS in trial of early ART versus delayed ART and all received BCG vaccination after birth [136]. BCG-IRIS developed in 32 [8.7%] of infants within 6 months of ART therapy, 88% within the first 2 months, and mainly as regional adenitis. Low CD4+ counts and high HIV-1 RNA were the strongest risk factors for BCG-IRIS.

Other forms of HIV-IRIS reported in tropical and subtropical countries include leprosy reactions, leishmaniasis-IRIS, and schistosomiasis-IRIS [137, 138]. Whereas, in industrialized countries, autoimmune diseases such as sarcoidosis, multiple sclerosis, and Grave's disease can appear as immune restoration diseases after ART therapy in HIV-infected subjects [139]. Also IRIS in HIV subjects can present with a severe drug hypersensitivity reaction, including drug reaction with eosinophilia and systemic symptoms [DRESS] and Sweet syndrome [140–142].

2.5.5 Management of HIV-IRIS

Treatment of HIV-IRIS should depend on the severity of disease and subtype of infections associated with the reaction. Although corticosteroids are commonly used for IRIS management, it has only been proven to be of benefit in one randomized trial of patients with TB-IRIS. In a placebo-controlled, randomized trial of 110 participants with paradoxical TB-IRIS, half were treated with prednisone for 4 weeks and a half with placebo. Prednisone was found to reduce the need for hospitalization and therapeutic procedures and resulted in clinical improvements of symptoms and quality of life, but was associated with greater risk of secondary infections [143]. For non-tuberculosis or MAC-IRIS, corticosteroids have been used in case series with some reports of benefit, but non-steroid anti-inflammatory drugs [NSAIDs] and surgical drainage or node excision have also been used [144].

Corticosteroids systemically have generally been avoided in viral-induced IRIS such as CMV-IRIS, but have been used for HIV-associated T cell encephalitis [HIV-neuro-IRIS] with reported clinical improvement in case reports [145]. Locally administered repository corticosteroids, most commonly in the sub-Tenon space, have been reported to improve vision in 9 of 10 patients with CMV-RIS [146].

CM-IRIS is associated with excess morbidity and mortality, and optimal therapy is unclear. Measures to control high intracranial pressure [when above >25 cm] should include repeated CSF drainage [15–20 mL daily or alternate days] and lumbar drain if this is unsuccessful. Although corticosteroids have been used with reports of symptom improvement, they should be avoided. In a randomized placebo-controlled trial of dexamethasone in CM [not specifically IRIS], treatment was

associated with greater disability, adverse events and delayed fungal clearance than placebo [147].

For PML-IRIS corticosteroids are best avoided as the paradoxical reaction appears to improve the resolution of PML, and these drugs should be reserved for severe neurological deficits such as cerebral edema or signs of impending brain herniation. Corticosteroids should also be avoided in KS-IRIS as their use can result in progression and worse outcomes. ART should be continued, chemotherapy and localized radiation maybe used to control the disease.

In cases of Hepatitis B or C-IRIS, corticosteroids, or other immunosuppressive are not recommended [144]. ART therapy maybe temporarily interrupted for hepatic decompensation and fulminant liver failure and all potentially hepatotoxic drugs discontinued. In hepatitis B coinfection, an active HBV drug should be continued to prevent viral rebound. ART can be restarted once the liver enzymes are returning to normal and the HBV DNA is falling. It has been suggested [but unproven] that high-risk patients for IRIS [very low CD4+ counts and high hepatitis viral load] with underlying cirrhosis may benefit by first starting treatment for the hepatitis virus to reduce the viral load before initiating ART.

2.6 Discussion and Future Directions

The proposed criteria for unmasking HIV-IRIS by Haddow et al. [71] should have a set time after starting ART [for the incubation period] before considering or labeling as IRIS, rather than just within 3 months when immune restoration is expected or shown to occur. It is unlikely that immune restoration would occur just after 1 week of ART. There is also a need for an international consensus guideline or definition of HIV-IRIS that is recognized by the WHO.

It is unlikely that large therapeutic trials can be conducted for any form of IRIS because of their infrequency. However, pilot studies should be conducted with new anti-cytokine drugs [being used for inflammatory conditions] for serious reactions where corticosteroids are not recommended. Tocilizumab, an inhibitor of IL-6 used for rheumatoid arthritis, maybe a suitable therapeutic candidate for severe IRIS. Thalidomide [not marketed] and minocycline have anti-inflammatory and immune modulation activities and are other potential drugs for IRIS, especially for KS or PML-IRIS. Minocycline would be particularly worthwhile assessing in prospective pilot trials of severe PML-IRIS, in view of its mechanisms of action and recent evidence of some benefit in early multiple sclerosis [148].

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Chapter 3
Issues in Community-Acquired Pneumonia

3.1 Introduction

Community-acquired pneumonia [CAP] is a common infectious disease encountered in all communities of the world, most frequently affecting the very young and the elderly. It is associated with significant mortality and morbidity in severe cases and pneumonia is the third most frequent cause of death worldwide [1]. However, statistics on the global or regional incidence and economic burden of CAP is lacking. It has been estimated that 4–6 million cases of CAP occur each year in the USA and approximately 20–25% require hospitalization [2, 3]. In the USA, CAP in all ages account for about 10 million physician visits annually and 600,000–1.1 million hospitalization each year with an estimated cost of over $17 billion annually [4, 5]. In Holland, it has been estimated that the incidence of CAP average 295 per 100,000 population per year and cost $711 [European Union] million over 4 years, total population of 16–17 million [6]. However, this analysis only included direct costs from hospitalization and not indirect economic burden from loss of employment. Limited data is available for the incidence and economic burden of CAP in the working-age population [age 18–64 years]. In a study from the USA, the overall incidence rate of CAP in this low-risk group was 10.6 per 1000 person years and 19.5% required hospitalization [7]. The average annual incremental cost ranged from $39,889 to $113,837 for inpatient management of patients with CAP and from $4170 to $31,524 for outpatient management.

3.2 Airway Defenses and Pathogenesis

The nasopharynx and the normal respiratory tract provide a complex series of mechanisms to protect the lower respiratory tract from noxious agents and microbial pathogens. Initially this includes the aerodynamic barriers of the nasopharynx,

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cough reflex, and mucociliary clearance of foreign material and invaders of the tracheobronchial tree. Local production of immunoglobulins [IgA, IgG, and IgE] in the mucosa of the respiratory tract provides another layer of protection against invading microbes. The relative proportion of IgA and IgG in the respiratory tract changes with the location, greater ratio of IgA to IgG in the nasal mucosa, trachea and bronchial tree and reversed ratio in the alveoli with greater proportion of IgG [8]. IgA may be more important in protecting against viral infections, as it can neutralize several respiratory viruses such as rhinovirus, influenza, and respiratory syncytial virus [8]. But it may be involved in the mechanisms of preferential bacterial adherence. Whereas, most individuals with IgA deficiency do not have increased respiratory infections, those with IgG or certain IgG subclass deficiency have recurrent respiratory infections [8].

IgG limits the invasion of microorganisms in the epithelium by opsonization and complement fixation and the concentration can increase a hundred-fold in the respiratory tract in the presence of infection and increased vascular permeability. Protection of the respiratory tract from microbial invaders is a complex process that involves many immune cells: dendritic cells, B and T-lymphocytes, neutrophils and macrophages and their secretory products [immunoglobulins, cytokines, opsonins, enzymes, and oxygen metabolites]; and nonimmune opsonins such as surfactant, fibronectin fragments, and possibly C-reactive protein [8]. Recent studies indicate that progranulin, an autocrine growth factor expressed in a variety of tissues and cell types, plays a protective role in lung immunity during bacterial pneumonia [9]. Elevated progranulin levels were observed in clinical and experimental bacterial pneumonia and it mediated host defense in both Gram-positive and Gram-negative bacterial pneumonia.

The healthy mucosa is colonized by a complex milieu of microorganisms, not exclusively aerobic and anaerobic bacteria, that probably plays an important protective role against invading pathogens. These normal microbes prevent the establishment of invading pathogenic microbes in the respiratory epithelium, the first step to induce infection. In the past decade, there has been marked interest and research on the role of the normal microbiome of the respiratory tract in health and disease. This has been facilitated by modern sophisticated, molecular, multiomics techniques. Recent studies of the human microbiome, including the respiratory tract, have demonstrated that the resident microflora is much more abundant and diverse than previously realized; including many species of nonculturable bacteria, viruses [virome], fungi, and protozoa. Present data indicate that the microbiome of the gut and the lungs are linked, by immune cells and mediators, and maybe important and associated with the pathogenesis of respiratory diseases [10–12]. The bronchial tract harbors a complex and dynamic microbial milieu of about 500 species, which overlaps with the oral microbiome [10]. The lung is also colonized by airway microbiota that resembles the microbiome of the mouth but not the nostrils at a lower density. Studies [10–12] have linked dysbiosis of the respiratory microbiome with asthma and chronic lung diseases such as cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease [COPD]. However, there is no data as yet on association with acute pneumonia.

It is generally believed, that CAP occurs from aspiration of pathogenic microbes colonizing the nasopharynx in situations where there is defect of the normal airway defenses. Inciting factors that may play a role in the development of pneumonia include preceding viral upper respiratory tract infections [seen in nearly 50% of bacterial CAP]. These minor infections can result in defect in mucociliary function and clearance of aspirated bacteria and allow adherence of pathogens to the mucosa. It is quite possible that upper respiratory virus infections can result in dysbiosis of the commensal respiratory microbiome. Cigarette smoking can have a similar effect on airway defense and has been associated with dysbiosis of the resident microbiota.

3.3 Microbial Etiology of Community-Acquired Pneumonia

Although numerous microorganisms can cause lung involvement or pneumonia [estimated about 100], only several have been associated with CAP in children or adults. In clinical practice the identification of etiologic microbes in CAP is usually achieved in <30% of cases. Sputum cultures are often nonspecific and difficult to interpret because of contamination of oral-pharyngeal commensals, and blood cultures are positive in only 5–14% of adults and even less in children with bacterial pneumonia [13]. Urinary antigen detection of *Streptococcus pneumoniae* may improve the sensitivity compared to culture [70–80% sensitive], but can be false positive from colonization in children [14]. In recent years studies have applied molecular assays for viruses and bacteria for microbial diagnosis. Results have indicated that the etiology of CAP may vary with age.

In children <5 years of age CAP is most commonly due to viruses [mainly respiratory syncytial virus or RSV], especially in the absence of lobar consolidation and effusion [15]; but even with extensive testing a pathogen cannot be identified in 14–23% of children with CAP [16, 17]. In a recent study of 70 children <5 years of age hospitalized for CAP without an identifiable etiology and 90 asymptomatic controls, metagenomics [next-generation sequencing] and pan-viral PCR were able to identify a putative pathogen in 34% of unidentifiable cases from nasopharyngeal and oropharyngeal swabs [18]. Putative viral pathogens included human parainfluenza virus 4, human bocavirus, Coxsackieviruses, and rhinovirus A and C. Human bocavirus was the most commonly detected virus [19%]. It is plausible that these viruses were causing upper respiratory tract disease that resulted in CAP from bacterial pathogens. Although cultures and PCR for bacterial pathogens were obtained, endobronchial secretions were not routinely obtained. In a meta-analysis of detection of viruses by PCR in childhood CAP, the pooled incidence was 57.4% with mixed infection in 29.3% [19]. Rhinovirus, RSV, and bocavirus were the three most common viruses in childhood CAP. Respiratory viruses were detected in 76.1% of patients aged ≤1 year, 63.1% of patients 2–5 years, and 27.9% of children aged ≥6 years [19]. It was estimated that more than half the viral infections were probably concurrent with bacterial infections. The etiology inference of identifying viruses in the upper respiratory tract in children with CAP is still unclear. Although higher viral loads can

be found in children with pneumonia compared to controls with some viruses, the utility to diagnose viral pneumonia with quantitative PCR was equivocal [20].

It is still the opinion of experts that most CAP in children with radiographic alveolar infiltrate is due to bacteria, predominantly *S. pneumoniae*. Previous studies have reported an association of upper airway density of *S. pneumoniae* and pneumococcal pneumonia, and nasopharyngeal bacterial load with this pathogen is significantly higher in viral infection compared with no viral infection [21]. In a case-control study from seven developing countries, colonization density of *S. pneumoniae in the upper* airway was compared in children [<5 years of age] with proven pneumococcal pneumonia and controls [22]. Pneumococcal colonization density >6.9 $\log_{10}$ copies/mL was strongly associated with confirmed pneumococcal pneumonia, with a sensitivity of 64% and specificity of 92% but not sufficiently accurate for clinical diagnosis. The same group of investigators also assessed the colonization density in the upper respiratory tract and confirmed pneumonia with *Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and *Pneumocystis jirovecii.* There was an association of colonization density [5.9 $\log_{10}$ copies/mL] and *H. influenzae* confirmed pneumonia, with a sensitivity of 86% and specificity of 77%, but not with the other respiratory pathogens [23].

In adults, the microbial diagnosis of CAP with conventional microbiology, urine antigen detection and commercial PCR for viruses in two prospective studies in the USA have had low yield [24, 25]. Each study failed to identify a respiratory pathogen in about 55–62% of cases, pneumococci was found in <10% of cases, respiratory viruses in 20–27%, and atypical organisms in about 5% of cases in one study [25]. A prospective study of 505 hospitalized patients with CAP in the Netherlands, using similar investigative techniques but added real-time PCR for "atypical organisms" *[Mycoplasma pneumoniae, Legionella pneumophila, Coxiella burnetii, and Chlamydophila* sp.], identified *S. pneumonia* in 25%, *C. burnetii* in 6%, *H influenzae* in 5%, and atypical bacteria including Legionella in 9% [26]. Some European studies have used advanced microbiological techniques with identification of pneumococcus in 30–64% of cases and identification of a pathogen in 63% of cases [27, 28]. In Norway, bacterial etiology was found in 47% and viruses in 34%, including viral–bacterial coinfections [28]. A prospective study from China, beside viral culture and nucleic acid amplification assessed paired sera for antibody response, and viral etiology was established in 34.9% of CAP [29]. In a review and meta-analysis of the incidence of viral infections in adult CAP, incidence ranged from 8.6 to 56.2%; lower tract samples were associated with higher viral yield and the three main viruses were influenza virus, rhinovirus, and coronavirus [30]. In a similar review by other investigators, the pooled proportion of patients with viral infection was similar, 24.5%, but in studies that obtained lower respiratory samples the proportion increased to 44.2% [31].

More recently in Britain, 325 adult patients with confirmed pneumonia admitted to two tertiary-care hospitals had cultures and comprehensive molecular testing [multiplex real-time PCR for 26 respiratory viruses and bacteria] from sputum [96%] and endotracheal aspirate [4% or 13 cases] [32]. An etiology agent was identified in 87% with molecular testing compared to 39% with culture-based methods.

Bacterial pathogen was detected by PCR in 78% and culture in 32% but most patients [85%] received antibiotics before admission. Viruses were present in 30% of cases but 82% were co-detected with bacterial pathogens. It was surprising that *H. influenzae* was the most common bacteria in 40.2%, followed by pneumococcus in 35.6%, *M. catarrhalis* in 13.6%, *S. aureus* in 10.2%, *Klebsiella pneumoniae* in 4%, and atypical organisms in <5% [32]. It is questionable that mere detection of a pathogen is sufficient to attribute causality, unless there is evidence of acute immune response, as most specimens were sputa and not aseptically collected endotracheal secretions. The high incidence of *H. influenzae* could represent oropharyngeal colonization with non-typeable strains, high prevalence of COPD [about 40%] and high proportion of older patients above 65 years of age [56.3%]. The low prevalence of atypical organisms [mycoplasma and *Chlamydophila pneumoniae*] is not surprising as the patients had severe pneumonia requiring hospitalization. It is likely that mild–moderate CAP receiving ambulatory treatment would have a higher proportion of the atypical bacteria. A similar but smaller study in Japan used conventional methods and real-time PCR for diagnosis of CAP [$n = 92$] from sputa and nasopharyngeal swabs; molecular methods detected a causative organism in 72% versus 57% with conventional methods [33]. *S. pneumoniae* was most frequently identified, followed by *H. influenzae* and *M. pneumoniae* [5%].

Pneumococcus is the most important bacterial cause of CAP, responsible for most CAP mortality in severe cases, but rates of detection have varied from 8 to 48%. Rapid diagnosis of pneumococcal etiology could lead to initiating treatment with a narrow-spectrum antibiotic such as penicillin, which would be cost saving, with decreased risk of superinfection with *Clostridium difficile* and lower rate of predisposing to multiresistant bacteria. Sputum Gram stain at presentation is an inexpensive, rapid, easy to perform test that is underused in clinical settings to assist in the diagnosis and treatment of CAP. In a prospective study of 670 patients with pneumonia [328 CAP], the utility of sputum Gram stain was assessed from 478 good quality samples [34]. The sensitivity and specificity of Gram stain were 62.5% and 91.5% for *S. pneumoniae*, 60.9% and 95.1% for *H. influenzae*, 68.2% and 96.1% for M**.** *catarrhalis,* 39.5% and 98.2% for *K. pneumoniae*, and 9.1% and 100% for *S. aureus*. Unfortunately about 30% of patients with pneumonia had no or poor quality sputum, which limits the overall diagnostic value. Hence, this simple test should be routinely used in the diagnosis of CAP whenever purulent sputum is available. Detection of pneumococcus C-polysaccharide in urine by immune chromatography is increasingly being used for evaluation of patients with CAP. In a large observational, multicenter, prospective study of 3874 patients admitted to hospital for CAP, pneumococcal infection was diagnosed in 21%, with 71% of the cases diagnosed exclusively by urinary antigen test [35]. The sensitivity and specificity were 60% and 99.7%, respectively. A combination of different methods, however, appears to be more sensitive. Using quantitative [q] PCR on blood samples, multiplex immunoassay for urine antigen and multiplex immunoassay for serologic antibody responses against 14 serotypes were able to detect pneumococcus in 47% of cases and 56% more patients than conventional methods [36]. The qPCR of blood samples, however, was not more sensitive than blood culture.

3.3.1 Comments on Microbial Etiology

How can we interpret these studies utilizing comprehensive molecular methods for etiology diagnosis of CAP? Finding viruses or pathogenic bacteria from nasopharyngeal and sputum specimens may not prove of causality in pneumonia, as they clearly can just be causing upper tract infection or colonization without producing lower respiratory disease. However, the absence of any specific pathogens from theses assays can effectively exclude them as etiology agents, since nearly all CAP is a result of aspiration of upper airway microbes. A combination of tests such as sputum Gram stain and culture, blood culture, urinary antigen and antibody response to the microbe[s] may be the most specific and reliable methods of determining causality, but are not highly sensitive nor provide rapid results to affect management. Future research should focus on rapid, readily available, and inexpensive tests for etiologic diagnosis of CAP that could be used in emergency departments. Such methods may use immunoassays that could detect various bacterial pathogens or antigens semiquantitatively from sputum, blood, and urine in the form of a dipstick, similar to that of a urinalysis test.

3.4 Diagnosis of CAP

In most cases of CAP, the diagnosis should be straightforward, but since the advent of chest radiograph there has been no significant advance in diagnostic methods. Typical mild cases of CAP with clinical symptoms of recent cough, fever, and the presence of chest crackles may be treated empirically without a chest X-ray or blood tests. However, normal chest examination can be present in about 50% of CAP. Chest radiograph is the standard investigation to confirm pneumonia in suspected cases and should be done in moderate–severe CAP even in the presence of typical chest findings, to define the extent of lung[s] involvement, assess for presence of parapneumonic effusion or possible empyema, and the presence of pulmonary cavitation or abscess. The presence of necrotizing pneumonia restricts the etiologic diagnosis to a few bacteria and usually requires a longer duration of therapy.

Diagnosis of CAP can be difficult in some more complicated cases, often severe cases with multi-organ failure or dysfunction requiring intensive care. In these situations, the difficulty lies in the interpretation of the chest X-ray. Problems arise from differentiating pneumonia from pulmonary edema, hemorrhage, atelectasis, and acute respiratory distress syndrome [ARDS]. Computerized tomography [CT] scan may or may not be able to differentiate these conditions. Bedside ultrasonography has been used for diagnosing pneumonia but is less reliable than radiography, with sensitivity ranging from 57% to 100% and specificity of 54% to 99% [37]. Ultrasound is more useful for defining the presence and severity of associated pleural effusion. Investigators have also assessed the value of molecular biomarkers in severely ill patients to differentiate CAP from noninfectious cause of lung infiltrates. In a study

of 234 patients admitted to the intensive care unit [ICU] with suspected CAP genome-wide transcription profiling of blood leucocytes was investigated. Expression of proinflammatory and anti-inflammatory pathways was similar between patients with and without CAP, and blood concentrations of biomarkers such as procalcitonin, interleukin [IL]-6, and interleukin IL-8 were not discriminatory [38]. Further analysis revealed that the ratio of two genes, FAIM3 and PLAC8, was best for distinguishing CAP from no-CAP. The FAIM3:PLAC8 ratio provided a positive predictive value of 83.1% and negative predictive value of 81.3%. However, the clinical utility for management in seriously ill patients is questionable and further studies are needed.

3.5 Markers of Prognosis of CAP

The risk of CAP and invasive pneumococcal infection in adults increases with older age, number of comorbidities, cigarette smoking, and the combination of the above [39]. Proton pump inhibitors [PPI], a commonly prescribed medication, in this high-risk population also may add to the risk of CAP. A systematic review of 26 studies with 226,769 cases of CAP reported a 1.5-fold increased risk of CAP, with the highest risk in the first 30 days after initiating a PPI [40].

CAP is the most common infectious disease leading to hospitalization in the ICU and the leading cause of mortality in patients with infection [41]. Severe sepsis may be present in about one-third of patients presenting with CAP at a hospital. Predictors of severe sepsis and assessment for these factors are important on arrival in the emergency department [ED], to facilitate rapid treatment and close monitoring to avoid high fatality. In a prospective multicenter cohort study of 4070 hospitalized CAP patients, 37.6% presented with severe sepsis [42]. Severe sepsis with CAP was independently associated with age >65 years, alcohol abuse [odds ratio [OR], 1.31], COPD [OR, 1.75], kidney disease [OR, 1.57], *S. pneumoniae* [OR, 1.59], mixed microbial etiology [OR, 1.65], and bacteremia [OR, 1.37]; whereas prior antibiotic treatment was protective [42].

Other comorbid conditions such as cardiovascular disease may not predispose to severe sepsis but may result in higher mortality and morbidity. Previous studies indicate that CAP is associated with increased cardiovascular complications. In a multicenter prospective cohort of 1182 patients hospitalized for CAP, 32.2% experienced cardiovascular complications, including heart failure [23.8%], atrial fibrillation [9.2%], myocardial infarction [8%], ischemic stroke [0.9%], and deep vein thrombosis [0.1%] [43]. The 30 day mortality was significantly higher in patients who developed cardiovascular complications compared to those who did not [17.7% versus 4.55%, $p < 0.001$]. Studies have also reported increased mortality in patients with vitamin D deficiency [44] and extreme thinness [body mass index <16/kg/m^2] on developing CAP [45].

Various scoring systems and biomarkers have been developed to identify severe CAP, assess prognosis for mortality risk and to assist physicians in making decisions

Table 3.1 CURB-65 score

	Factors assessed	Total score (1 per factor)	Mortality risk (%)
1.	Confusion [mental test or disorientation]	0	0.7
2.	Urea [BUN >7 mmol/L or 20 mg/dL]	1	2.1
3.	Respiratory rate ≥30/min	2	9.2
4.	Blood pressure [systolic <90 or diastolic ≤60]	3	14.5
5.	Age ≥65 years	4	40

BUN blood urea nitrogen
Disposition of patient based on total score: 0–1 treat as outpatient; admit to hospital for 2 and above

on hospital and ICU admission. These scoring systems were designed for the use in non-immunosuppressed patients. The most commonly used scoring system is the CURB-65 score, which is based on five easily measurable factors [see Table 3.1]. The presence of each factor was given a score of 1 to a maximum of 5. In the initial study of 718 patients in the derivation cohort and a separate validation cohort, the 30 day mortality was 0.6–0.7%, 1.7–2.1%, 9.2%, 14.5%, and 40% for 0, 1, 2, 3, or 4 factors [46]. Based on these data, it was suggested that that CAP patients with a score of 0–1 could be treated as outpatients, those with a score of 2 should be admitted to hospital, and those with a score of 3 or more should be assessed for ICU care. However, another large study of 3181 patients with CAP reported a mortality of 3.0% with a CURB-65 score of 1 [47]; which suggests even 1 score should be an indication for hospital admission. But a healthy 65-year-old person without other factors or significant comorbid illness could be treated with outpatient antibiotic. In a more recent study, however, CURB-65 had very good accuracy for predicting the 30-day mortality among 7952 patients with CAP discharged from the ER [48]. Among all ER encounters the CURB-65 threshold of >1 was 92.8% sensitive and 38.0% specific for predicting mortality, with a 99.9% negative predictive value.

A simplified version without blood test to measure blood urea nitrogen [BUN], designated CRB-65, can be used in the doctor's office to assess severity of CAP. If I or more score is present then the patient is referred to the hospital for admission. The CRB-65 score has not been extensively evaluated but was found to have good predictive value in 670 patients with CAP [49].

The Pneumonia Severity Index [PSI] assessment is based on the presence of 20 variables and is divided into five strata of increased risk for short-term mortality at presentation [50]. Low-risk patients with cumulative mortality of <1% falls in the class I-III, whereas patients in class IV and V have higher mortality risk of 9% to 30%. Although several large studies have validated its predictive utility, it is more complex to calculate, less user friendly than CURB-65, and the predictive performance is similar in prospective comparison [47]. Hence, CURB-65 is more commonly used by ED physicians to assess CAP severity. The British Thoracic Society and the National Institute for Health and Care Excellence [NICE] guidelines recommend CURB-65 and CRB-65 for severity assessment in CAP [51, 52].

For patients hospitalized for CAP risk prediction can be used to assess the need for ICU care, mechanical ventilation, and mortality. Monitoring the C-reactive protein [CRP] during hospitalization may be useful in predicting response and the risk of death. In a retrospective multicenter study of 814 patients with CAP admitted to three Dutch hospitals, the highest mortality risk was seen in patients who failed to demonstrate a decline in their CRP by 50% after 3 days of treatment, irrespective of the actual value and initial CURB-65 score [53]. This study should be validated by a larger prospective study.

Three scoring systems have been developed to identify severe CAP in hospital and the need for ICU management. These include the severe community-acquired pneumonia score [SCAP], SMART-COP, and the Infectious Diseases Society of America/American Thoracic Society [IDSA/ATS] severity criteria [see Table 3.2]. All three systems utilize a combination of clinical criteria [shock, altered mental state, and respiratory failure], routine blood tests, and arterial blood gas results. A SCAP score of ≥10 [at least one major and two minor criteria] was superior to CURB-65 in predicting progression to more severe pneumonia [54]. Further validation study showed that the SCAP score was just as accurate as other prediction scoring systems for predicting ICU admission, progression to severe sepsis, treatment failure and need for mechanical ventilation [55]. The SMART-COP scoring system was assessed in a prospective study of 882 episodes of CAP requiring hospitalization, with more than 75% of patients over 50 years old [56]. Each factor led to accrual of one point, except low systolic blood pressure, poor oxygenation, and low arterial pH, each subscribed two points. SMART-COP score of ≥3 points identified 92% of patients who received intensive respiratory or vasopressor support [56]. The predictability of SMART-COP was less accurate in younger adults <50 years of age, as it failed to identify the need for these critical measures in 15% of patients in this age group [57]. The IDSA/ATS severity system is based on two major criteria and nine minor criteria [58]. Any one of the major criteria, septic shock requiring vasopressors and requirement for mechanical ventilation, are universally accepted and are self-evident. Three or more of the minor criteria indicate need for ICU management. A validation study of 1062 patients with CAP, not meeting the major criteria, found the minor criteria were equivalent to the SMART-COP scoring system for predicting need for mechanical ventilation, vasopressor support, and ICU care [59]. Recently, other investigators have modified the IDSA/ATS minor criteria by excluding four infrequent variables [leucopenia, hypothermia, hypotension, and thrombocytopenia] but adding age ≥65 years [60]. The modified version best-predicted mortality, but it is unclear whether it is as useful for predicting need for ICU care and vasopressor/ventilation support.

Various blood biomarkers have been studied as prognostic predictors in CAP and these include procalcitonin [PCT], CRP, proadrenomedullin [pro-ADM], presepsin [sCD14-ST], copeptin, and cortisol. The PCT was the most extensively studied in a total of 21 studies with 6007 pneumonia patients. Although elevated PCT level was a risk factor for death in CAP, particularly patients with a low CURB-65 score, the commonly used cutoff, 0.5 ng/mL, had low sensitivity in identifying patients at risk of dying [61]. In a systematic review and meta-analysis of the prediction value of

Table 3.2 IDSA/ATS guidelines for ICU management

Major criteria [any one]
Septic shock requiring vasopressor support
Respiratory failure needing mechanical ventilation
Minor criteria [≥3]
1. Altered mental status
2. Hypotension requiring fluid support
3. Temperature <36 °C [96.8° F]
4. $PaO_2/Fi0_2$ ratio ≤250
5. Blood urea nitrogen ≥20 mg/dL or 7 mmol/L
6. Leucocyte count <4000 cells/μL
7. Platelet count <100,000/mL
8. Multilobar infiltrates

PaO_2 arterial oxygen concentration, *FiO_2* fraction of inspired oxygen or percentage by decimal fraction
With nasal cannula or simple face mask each liter/min of oxygen provides 4%/L for the first 3 L and only 3%/L thereafter to their FiO_2. Example: nasal cannula with 4 L/min oxygen flow provides an FiO_2 of 21% + [3 × 4%] + [1 × 3%] = 36%—expressed as 0.36 for calculation

various biomarkers in 10,319 CAP patients, they demonstrated moderate–good accuracy to predict mortality but had no clear advantages over CAP-specific scores [62].

3.5.1 Comments on Prediction Scores

CURB-65 should be the standard prediction score applied to patients seen in hospital ED with CAP, the main contentious issue is whether or not patients with a score of 1 should be admitted or treated as outpatients. It may be reasonable to admit patients with one factor, other than age 65 years alone. Using age alone for admission has no supporting evidence for almost every medical illness. However, patients 65 years or older with significant comorbid illness, such as underlying cardiovascular disease, should be admitted and monitored. Once patients are admitted to hospital the IDSA/ATS guidelines maybe the most appropriate to use on deciding on further care in the ICU, although SCAP and SMART-COP scores are suitable as well.

3.6 Treatment of CAP

Empiric treatment of CAP is designed to treat common bacterial respiratory pathogens [*S. pneumoniae, H. Influenzae]* and atypical bacteria [*M. pneumoniae, C.pneumoniae*], but recent etiology studies suggest that a large proportion of CAP is due to

viruses alone in both children and adults. Hence, an accurate test available in any hospital that could differentiate viral from bacterial infection would be cost saving and decrease overuse of antibiotics. Serum PCT levels has been studied for this purpose. PCT concentration, cutoff value 0.10 ng/mL, has been used in 453 patients to differentiate acute heart failure from pneumonia in the ED [62]. The median PCT level was significantly higher in patients with pneumonia than in those without [0.38 ng/mL versus 0.06 ng/mL]. Among patients with >75% clinical likelihood of heart failure, PCT value of 0.10 ng/mL had a sensitivity for identifying pneumonia of 95% and a negative predictive value [NPV] of 99%; but for patients with low likelihood of heart failure, the PCT cutoff value had 85% specificity and 95% NPV [63]. In a large prospective multicenter study of 1735 adult patients with CAP, the accuracy of PCT concentration to discriminate between bacterial and viral pathogens was estimated [64]. Pathogens were identified in only 37%, including 10% with typical bacteria, 4% with atypical bacteria, and 24% with viruses only. The median PCT concentration was lower with viral pathogen [0.09 ng/mL], than atypical bacteria [0.2 ng/mL] and typical bacteria [2.5 ng/mL]. A PCT value of 0.1 ng/mL resulted in 80.9% sensitivity and 51.6% specificity for any bacterial pathogen. No PCT threshold discriminated viral from bacterial etiology with a very high sensitivity and specificity [64].

A contentious issue in the empiric management of CAP is the routine coverage for atypical bacteria with a macrolide, as *M. pneumoniae* and *C. pneumoniae* infection are usually associated with self-limited course and recovery. Whereas, North American guidelines for outpatient treatment of CAP list a macrolide as first choice [65] European guidelines do not [52] and consider macrolides as second choice for penicillin-allergic patients. Moreover, coverage for atypical bacteria routinely in the management of CAP has not been proven to be beneficial. In a systematic review of 28 trials and with 5939 randomized patients, no advantage was found for regimens covering atypical bacteria in the major outcomes tested—mortality and clinical efficacy [66]. Macrolide as a sole therapy for CAP maybe inadequate to cover pneumococcus, as the prevalence of macrolide resistance has been increasing and is currently up to 35%, although the clinical significance is uncertain [67].

For patients with moderate–severe CAP being hospitalized, North American and European guidelines [51, 52, 65] recommend initiating broad-spectrum therapy of a β-lactam agent [often ceftriaxone] and a macrolide or a respiratory quinolone alone. The macrolides have immunomodulatory effects and anti-inflammatory properties that may improve outcome even for pneumococcal infection. Even in Gram-negative sepsis and ventilator-associated pneumonia, clarithromycin has been reported to restore the immunoparalysis and improve outcome [68]. A recent systematic review of antibiotic therapy for hospitalized adults with CAP has been published [69]. Several key aspects of antibiotic therapy can be summarized: (1) eight observational studies showed that antibiotic initiation within 4–8 h of hospital arrival was associated with decreased mortality; (2) stepping down from intravenous to oral therapy once patients are stable shortens hospital stay without affecting outcome; (3) choice of empiric antibiotics on outcome was mixed and inconclusive. Six of eight low-quality observational studies [with up to 24,780 patients] found that the combina-

tion of β-lactam and macrolide was associated with reduced short-term mortality over β-lactam monotherapy. The three largest studies were all retrospective in design. Three observational, mainly retrospective, studies found reduced mortality with quinolone monotherapy compared to β-lactam monotherapy [69].

However, in prospective randomized, trials the results have not confirmed superiority of combination with a macrolide nor quinolone over β-lactam monotherapy. In the first trial in Switzerland, 580 adults with moderate–severe CAP admitted to six acute care hospitals were randomized to β-lactam monotherapy or a macrolide combination [70]. The mortality, ICU admission, length of stay, and recurrence of pneumonia within 3 months were not different between the treatments. In the second prospective multicenter Dutch trial, 2283 patients with CAP admitted to non-ICU wards were allotted to one of three treatments by a cluster-randomized, crossover design with strategies rotated in 4-months period [71]. Monotherapy with a β-lactam was non-inferior to strategies with β-lactam macrolide combination or quinolone monotherapy for 3 months mortality, length of stay, or any complications. Quinolones when used can be given orally from the onset if the patients can take oral medications, since they are fully bioavailable. IDSA guidelines had recommended initial intravenous therapy for severe pneumonia, but well-conducted observational study confirms that intravenous route is not necessary for severe CAP [72].

The duration of treatment for CAP is not well established. IDSA/ATS guidelines recommend at least 5 days treatment in patients who are stable and have been afebrile ≥48 h [65]; the British guidelines advice 7 days for mild–moderate and 7–10 days for moderate–severe CAP [51]; and the NICE guidelines recommend 5 days for mild and 7–10 days for moderate–severe CAP [52]. In a recent multicenter randomized trial from four teaching hospitals in Spain, the duration of antibiotic treatment was studied in 312 hospitalized patients with CAP [73]. After 5 days of treatment, the intervention group stopped antibiotics if they were afebrile for 48 h and had no more than one CAP-associated sign of instability, and the duration of antibiotics in the control group was determined by physicians. There was no significant difference in the outcome between the two groups. Thus, the IDSA/ATS guideline is safe to implement in hospitalized patients with CAP.

3.6.1 Comments on Treatment of CAP

Current data indicates that amoxicillin for outpatient treatment of mild–moderate CAP for 5 days is the preferred therapy. Macrolide monotherapy should be avoided due to high and rising resistance of *S. pneumoniae.* Furthermore, moderate macrolide resistance in *M. pneumoniae* has now been reported with analysis for resistant mutation genes [74]. *A*moxicillin/clavulanic acid maybe preferable to cover β-lactamase strains of *H. influenzae* and *M. catarrhalis* in the elderly and subjects with COPD or chronic bronchitis. Patients admitted to hospital for moderate–severe CAP, not requiring ICU care, can be treated with a β-lactam monotherapy [commonly ceftriaxone] but amoxicillin/clavulanic acid can be used or respiratory quinolone orally.

Whenever pneumococcus is shown to be the etiologic agent, penicillin should be used as there is no evidence that the outcome is adversely affected for penicillin non-susceptible [relative resistance] strains in CAP even with bacteremia.

In patients with severe CAP requiring ICU care, a β-lactam [ceftriaxone] with a macrolide or a quinolone alone is suitable. In this setting, the macrolide is used for *L. pneumophila* infection until this organism can be excluded.

3.7 Adjunctive Therapy for Severe CAP

Severe CAP has a high mortality [about 38%] despite adequate antibiotic therapy, thus adjunctive therapy has been studied and used empirically to try and improve the outcome. Combination with a macrolide for macrolide-resistant bacteria is a form of adjunctive therapy. Comparative studies on the inflammatory response of patients with severe and non-severe CAP can be useful to guide adjunctive therapy. In one such study, the severe CAP group showed higher plasma levels of pro- and anti-inflammatory cytokines but in contrast, lower sputum concentration of proinflammatory cytokines [75]. Moreover, neutrophils from severe CAP patients showed reduced respiratory burst activity compared to the non-severe group. These results indicate that patients with severe CAP fail to mount a robust local inflammatory response but instead produce a heightened systemic inflammatory response [75].

It has been suggested that statins, primarily indicated for dyslipidemia and cardiovascular disease, have modulation effects on the cytokine cascade and could be useful in severe CAP. In a previous review of the immunomodulatory effects of statins in CAP, 17 experimental and 17 clinical studies were identified [76]. Statins attenuated pulmonary inflammation by reducing cytokine release and expression, modulating neutrophil function, and by protecting against disruption of lung integrity. Observational studies suggested a decrease in mortality due to CAP in current statin users but randomized studies are lacking [76]. A randomized, double-blind, placebo-controlled trial of simvastatin for CAP was initiated in Spain but was terminated after enrolling 34 patients because of slow enrolment [77]. However, after 48 h of statin, there was no difference in concentrations of cytokines compared to patients on placebo. Thus, the benefit of statins in CAP remains unknown.

Corticosteroids [steroids] have been studied for its anti-inflammatory effect in severe CAP in an attempt to reduce mortality, ARDS and need for mechanical ventilation and ICU care with inconclusive results. Although steroids have been shown to improve outcome and decrease risk of respiratory failure in pneumocystis pneumonia, it failed to improve outcome in a major, definitive randomized controlled trial in patients with all cause sepsis [78]. In a previous review of this topic in 2014, it was concluded that steroids should not be used in CAP because of insufficient evidence of the beneficial effect and potential harm [79]. Since then, two other randomized, placebo-controlled trials of adjunct steroids in CAP have been reported. The first study from Spain randomized 120 patients to intravenous methylprednisolone or placebo for 5 days. There was less early treatment failure [composite end

points defined by the study] in the steroid treated group but no difference in mortality [80]. The second study from Switzerland randomized 785 patients to either prednisone 50 mg daily or placebo for 7 days. Prednisone shortened the time to clinical stability by about 1.5 days without an increase in complications but did not improve mortality [81]. In the past 2–3 years four systematic reviews and meta-analyses of the value of steroids in CAP have been published. In the first report, ten randomized controlled trials [RCT] with 1780 cases of hospitalized CAP were reviewed. Mortality was decreased in the severe-case subgroup and patients requiring ICU care. Length of ICU decreased by 1.3 days and length of hospital stay by 1 day [82]. In the second review in 2015, 12 trials were included with 1974 patients and concluded that steroids may reduce mortality by 3%, need for mechanical ventilation by 5%, and hospital stay by 1 day [83]. The third report only included 8 RCTs enrolling 528 more severe CAP patients. Results from this meta-analysis showed steroids significantly reduced mortality [$p = 0.003$], risk of ARDS [$p = 0.02$], need for mechanical ventilation [$p = 0.026$], and length of hospital stay decreased by 4.7 days [$p = 0.006$] [84]. In the final review, nine RCTs [1667 patients] and six cohort studies [4095 patients] were included in the analysis. Steroids treatment was associated with reduced ARDS and reduced length of ICU stay but no effect on mortality [85]. None of the four studies found significant adverse events with steroids except for hyperglycemia.

3.7.1 Comments on Adjunctive Therapy for CAP

In moderate–severe CAP adjunctive macrolide is not beneficial. Further randomized studies are still needed for the more severe cases at risk for ICU management. Steroids may be beneficial to reduce mortality, ARDS and mechanical ventilation for the severe CAP but the results are not conclusive. Thus, it would be premature to use steroids routinely in severe CAP, pending larger RCT in this subgroup of patients admitted to hospital. In the most recent review and meta-analysis of steroids in hospitalized patients with CAP, with analysis of 1506 cases from six trials, steroids reduced time to clinical stability and length of hospital stay by 1 day but did not reduce mortality and increased risk of hyperglycemia and CAP-related rehospitalization [86]. The state of the art is reminiscent of the data of steroids in sepsis/septic shock, when steroids appeared to be effective in reducing mortality based on small RCTs but was proven ineffective in larger, definitive trials. At least three large trials registered on Clinical Trials.gov are expected to enroll a total of 2300 patients and are scheduled for completion by October 2018 will provide more definitive data on the use of steroids in CAP. Future trials should investigate the effect of adding nonsteroidal anti-inflammatory agents [NSAIDS] for the treatment of CAP. In a recent open randomized trial from Hong Kong, patients hospitalized with severe influenza A [H3N2] with pulmonary infiltrates had significantly lower 30-day mortality and shorter hospital stay after treatment with naproxen–clarithromycin [2 days] + oseltamivir than oseltamivir, both groups received beta-lactam antibiotics [87].

3.8 Prevention of CAP

In the past 20–30 years, marked reductions in the total burden and mortality of pneumonia in children <5 years of age have occurred worldwide. This has been attributed to a number of factors, improved healthcare and social-economic conditions in low earning countries, and major contribution due to increased vaccination against measles, pertussis, *S. pneumoniae* and *H. influenzae* type b with conjugate vaccines. However, similar reduction in CAP has not been realized in adults. Smoking cessation may reduce the risk of CAP in chronic smokers but permanent cessation is difficult to achieve. The World Health Organization estimates that >1 billion of the world's population smoke and smoking is a strong risk factor for invasive pneumococcal disease and bacterial pneumonia [88].

In most temperate countries peak incidence of CAP occurs in the winter during the peak influenza season. Thus universal yearly influenza vaccination may decrease the incidence of CAP in children and adults for influenza and bacterial pneumonia. Previous studies have shown that influenza vaccination is effective in preventing hospitalization for acute respiratory illness associated with confirmed influenza. Estimates ranged from 53% to 67% among children, 54% to 71% among all adults, and 42% to 61% for adults 65 years or older [89–92]. However, most of these studies did not specifically assess the effect of influenza vaccination on the prevalence of CAP. In a prospective observational multicenter study of hospitalization for CAP over 2.5 years in four US sites, 2767 patients were hospitalized for CAP. Among children and adults, only those with confirmed influenza-associated pneumonia had lower odds of having received influenza vaccine [93]. Indicating that influenza vaccination reduces CAP from influenza complication, including secondary bacterial pneumonia.

The introduction of the 7-valent and subsequent 13-valent *S.pneumoniae* conjugate vaccine [PCV13] in children in resource-rich countries has resulted in the decline of pneumococcal pneumonia in children and adults as well, through herd protection [94]. The 23-valent pneumococcal polysaccharide vaccine [PPV23] has been available for >30 years and is recommended in many countries for high-risk patients, but its efficacy in preventing CAP is debatable. Three recent reviews and meta-analysis of the benefit of PPV23 in preventing pneumococcal CAP in adults have been published with inconsistent conclusions. One review found no proof that PPV23 can prevent pneumococcal CAP in the elderly population [95]. Another study reviewed seven randomized trials involving 156,010 subjects and concluded that the PPV23 vaccine provided weak protection against all cause pneumonia [96]. The third review, however, reported that PPV23 vaccine effectiveness in preventing invasive pneumococcal disease was 50% for cohort studies and 54% for case-control studies [97]. But lower for prevention of CAP, 4% reduction in trials, 7% for case-control studies and 17% effectiveness for cohort studies. However, the conjugate vaccine appears to be more effective in adults. In a large placebo-RCT involving 84,496 adults 65 years of age and older, the Community-Acquired Pneumonia immunization Trial in Adults [CAPiTA], the PCV13 vaccine was assessed [98]. The vaccine efficacy in preventing

vaccine-type pneumococcal CAP was 45.6% and 75% in preventing invasive pneumococcal disease, but not effective in preventing CAP from any cause.

3.8.1 Comments on Prevention of CAP

More effective treatment is clearly needed for smoking cessation worldwide to prevent lung cancer, cardiovascular disease, COPD and many associated cancers and illnesses, including possible CAP. Although universal annual influenza vaccination is now recommended for children and adults, the rate of vaccination in all countries has been low [<20–30% of the population]. Improved and more effective, long lasting influenza vaccines [given by nasal or oral route] are needed to facilitate greater compliance and herd immunity. In the meantime, physicians should encourage annual influenza vaccines for all. PCV13 should be offered to all elderly and high-risk adults for CAP. Pending the development and marketing of a 23-valent conjugate pneumococcal vaccine, it is reasonable to administer the PPV23 as well several months later.

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Chapter 4
Helicobacter pylori Infection: When Should It Be Treated?

4.1 Background

Helicobacter pylori [formerly *Campylobacter pylori*] bacteria were discovered in 1982 during investigation of peptic ulcer disease, isolated from gastric/duodenal ulcers of patients. This led to the revolution in the treatment of peptic ulcers and our understanding of the cause of gastric cancer. Genetic anthropogenic studies suggest that *H. pylori* have been present in humans for >60,000 years, before humans migrated out of Africa, between 88,000 and 116,000 years [1]. Phylogeographic studies indicate that the global distribution reflects ancient migration of early human communities with substantial genetic variability in different geographic areas [2]. Whole genome analysis of 60 globally distributed *H. pylori* strains suggests that the microorganism has been in humans at least twice as early as previously estimated, from the early development period of the genus *Homo* [3].

H. pylori are motile, curved, Gram-negative rods that grow in a microaerophilic environment and produces high amount of urease, oxidase, and catalase. The organisms live freely in the mucus and less amount adhere to the mucosa of the stomach [gastric antrum and fundus] and occasionally to ectopic gastric-like epithelial cells of the duodenum and esophageal epithelium [4]. Twenty strains of *H. pylori* are present and the individual may be colonized with more than one strain.

The global prevalence of *H. pylori* varies greatly, lower in industrialized countries and higher in developing countries and trends are related to socioeconomic development and sanitary conditions. A recent systematic review on the prevalence of *H. pylori* infection/colonization with data from 62 countries, estimated that there were about 4.4 billion people [>half the world's population] infected [5]. The highest pooled prevalence was in Africa [70.1%], followed by South America [69.4%], and Western Asia [66.6%] and the lowest in Oceania [24.4%], Western Europe [34.3%] and North America [37.1%]. Rates of infection with *H. pylori* have been declining for several decades in North America, Western Europe, and Japan, but

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remain high for the indigenous population of the Arctic regions and Siberia [6]. There are also significant differences within countries with prevalence greater in the lower socioeconomic strata of society and disadvantaged groups, Latinos, blacks, and native indigenous people of North America. In developing countries, acquisition of the bacteria occurs in childhood after the first year and by 10 years of age 70% carry the microorganism; but in North America rates are low in children [about 5%] and reaches 50% after 60 years of age [4].

4.2 Transmission

Humans are the primary or only reservoir of *H. pylori* and the bacteria can be found in the saliva and feces [4] and infection is predominantly transmitted within families [7]. Thus, transmission appears to be by intimate contact or by fecal–oral route [8]. Others have presented data to suggest that well water or contaminated water can be a source of *H. pylori* transmission [9, 10].

4.3 Pathogenesis

H. pylori is highly associated and considered to be the cause of most cases of peptic ulcer disease, chronic gastritis, gastric adenocarcinoma, and mucosa-associated lymphoid tissue [MALT] lymphoma. Unlike most bacteria*, H. pylori,* can survive the hostile acid environment of the stomach by its urease activity once it enters the host. The urease activity required for acid resistance is regulated by the proton-gated channel Urel, results in large amounts of urea-derived ammonia production and ammonia hydroxide neutralizes the acidic microenvironment surrounding the bacteria [11]. In addition, urease can modulate phagosome pH and megasome formation which can allow *H. pylori* survival in macrophages [12].

The bacterial flagella is another virulence factor that allows *H. pylori* to move through the gastric mucosa epithelium to the basal layer and is essential for colonization in the animal model [13]. Although there is evidence that the flagella do not play a direct role in adhesion to gastric epithelium [14], mutants of the flagella-associated regulator showed decreased adhesion to gastric cells [15]. *H. pylori* possess several adhesins to bind to cellular receptors present on gastric cells of which blood-antigen binding protein A [BabA] and sialic acid-binding adhesion [SabA] are the best characterized, but not all strains express these adhesins [16, 17]. BabA bind to fucosylated Lewis B blood group antigen expressed on host gastric epithelium and the expression contributes to increased risk of peptic ulcer and gastric cancer in Western countries but not in Asians [18]. Neutrophil-activating protein [NAP] is another adhesin that promotes neutrophil and mononuclear cells infiltration of gastric mucosa, hallmark of chronic gastritis, and stimulate expression and

release of inflammatory proteins, interleukin [IL]-8, and reactive oxygen species that lead to local tissue damage [18].

H. pylori adhere to the gastric epithelium but do not invade the mucosa and in all colonized patients there is inflammatory infiltrate of the lamina propria with mononuclear cells—lymphocytes and monocytes [4]. The alteration in the gastric epithelium is secondary to extracellular products produced by the bacteria. The two main products associated with tissue damage are cytotoxin-associated gene A [CagA] protein and vacuolating cytotoxin A [VacA]. The prevalence of CagA-positive *H. pylori* in Western countries is about 60% and in Asian countries it is approximately 90% [19, 20]. CagA protein can be divided into Western-type CagA and East Asian-type CagA, based on the repeat sequence of the N-terminus of CagA. The East Asian-type CagA affinity for the SH2 domain, that aid in signal transduction of receptor tyrosine kinase pathways, is greater than the Western-type CagA, resulting in more cytoskeletal changes, and more likely to be associated with gastric cancer [21]. Alteration of the gastric epithelial cells is secondary to translocated CagA into the epithelial cells by the bacterial type IV secretion system [22]. Phosphorylated CagA interact with intracellular regulatory molecules that affect cells' shape and cycle events, resulting in increased proinflammatory cytokines leading to gastric mucosa inflammation, chronic gastritis, linked to epithelial dysplasia, metaplasia, and changes of gastric cancer [4].

VacA is embedded in the host cell membrane and can be endocytosed into the endosome and causes pore formation, mitochondrial disturbance, and apoptosis [23]. In addition, VacA can affect the genes that regulate cell cycle to disrupt the balance of cell proliferation and death and induce acute inflammation by inducing release of IL-8 [24]. All strains of *H. pylori* carry the *vacA* gene encoding the protein production with varying degrees of expression determined by the signal sequences of three regions [18]. The genotype can be divided into subtypes based on the combinations of the diversity of these three regions. Certain genotypes [s1/m1] expression of VacA is highly active and can cause acute cell damage. *H. pylori vacA* s1 and m1 strains are associated with high degree of gastric mucosa inflammation and increased risk of for gastric atrophy and cancer [25]. However, the association of *vac*A with disease is not consistently found in different countries, which suggest the importance of other factors, such as genetic host or environmental factors in disease manifestation. Figure 4.1 outlines the pathogenic mechanisms of *H. pylori* in relationship to clinical disease entities.

4.4 Clinical Disease and Associated Mechanisms

The commonest outcome of *H. pylori* infection is superficial gastritis and the majority of patients are asymptomatic. Acute symptomatic gastritis occurs after accidental or voluntary experimental ingestion of *H. pylori* [26, 27] but is not usually recognized clinically in subjects with acute spontaneous infection. The early stages of the disease show presence of inflamed gastric mucosa with neutrophil infiltration,

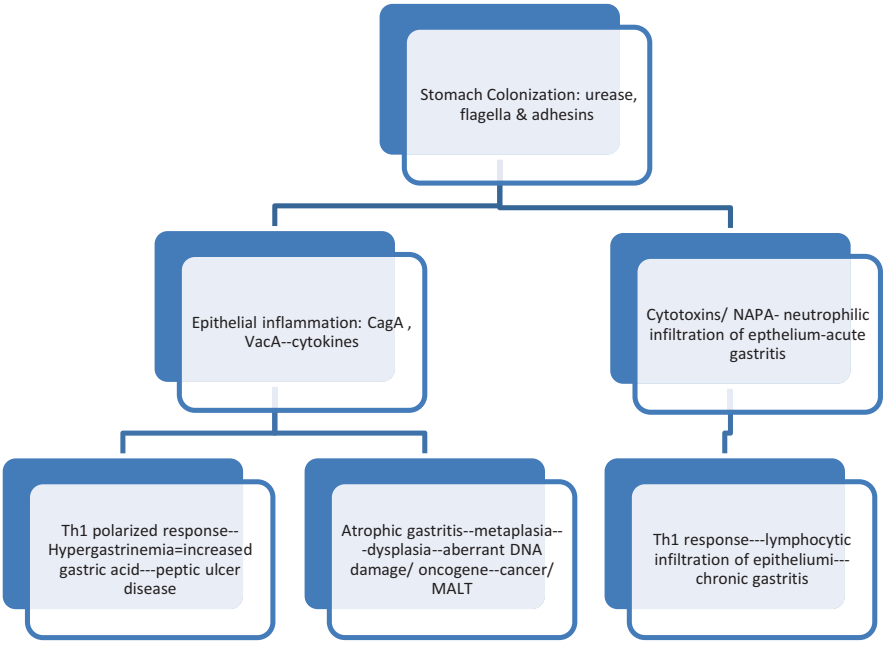

Fig. 4.1 Outline of the pathogenesis *of H. pylori* infection. *CagA* cytotoxin-associated gene A, *VacA* vacuolating cytotoxin *NAPA* neutrophil activating protein A

associated with dyspeptic symptoms, and a transient reduction of gastric acid. The symptoms and signs resolve spontaneously within 7 days [27], with persistent colonization of the gastric antrum mucosa with low levels of *H. pylori* and mild lymphocytic infiltration; typical features of chronic superficial gastritis that is most prevalent worldwide in *H. pylori* infected patients seen on gastric pathology [28]. These histological changes correlate with IgM- and IgG-seroconversion. These changes may persist for decades or indefinitely and in some people progression to gastric atrophy or dysplasia occur that may lead to neoplastic transformation. Figure 4.2 outline the course of *H. pylori* and clinical diseases.

Peptic ulcer disease is strongly associated with *H. pylori* infection, 6.8-fold greater than those not infected with the bacteria [29]. The reduced incidence of *H. pylori* infection in Western industrialized countries has also coincided with the reduction of peptic ulcer disease [30]. The mechanisms of *H. pylori*-induced peptic ulcer disease is incompletely understood but human studies indicate that predominant antral gastritis leads to enhanced gastrin secretion. This results in greater parietal cell mass of the gastric corpus and excess acid secretion that leads to ulceration [31]. Human studies suggest that these physiological changes are related to T helper-1 [TH1] polarized immune response [32]. CagA was the immunodominant antigen [Ag] recognized by the reactive T cells in patients with ulcers responsible for the polarized Th1 response; whereas in non-ulcer subjects there was a generalized Th1 and Th2 response to non-CagA antigens. This correlated with epidemiological

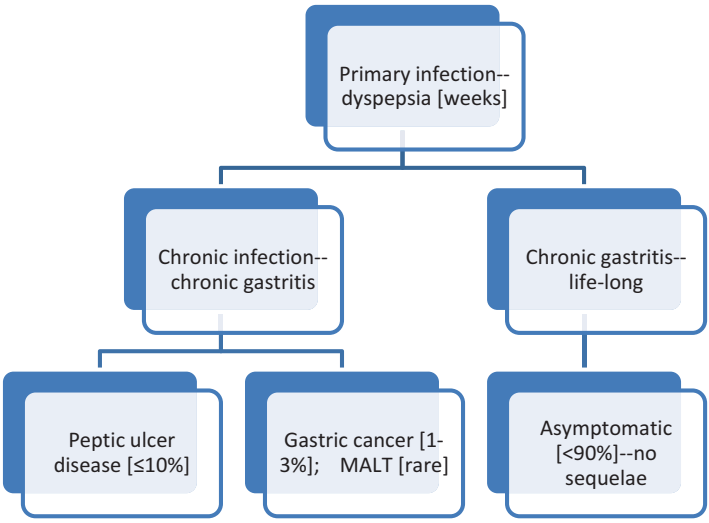

Fig. 4.2 Course and clinical disease from *H. pylori* infection. *Rare-associations*: unexplained iron deficiency and idiopathic thrombocytopenia

studies which found that patients with peptic ulcer have higher anti-CagA titers than non-ulcer patients [33]. *H. pylori* induce infiltration of T-lymphocytes, which triggers inflammation via chemokines and induce mucosal injury and apoptosis [34]. CagA-positive strains of *H. pylori* associated with peptic ulcer disease [>90%] also have high frequency of VacA, but 37% of patients with peptic ulcer are infected with *cagA* + $VacA^-$ strains [35].

Animal models have been used to study *H. pylori*-induced gastric ulcer with CagA-positive strains in gnotobiotic pigs, gerbils, and female C57BL/6 mice [28]. In the gerbil model, *cagE* [a gene of the *cagA* pathogenicity island] knockout prevented *H. pylori* from producing gastritis and gastric ulcer; *vacA* was not involved in the gastric mucosa inflammation but may be partially responsible for gastric ulcer formation [36]. In the mouse model, probiotic could eliminate *H. pylori* and reverse peptic ulcer disease [37]. Hence, it is likely that the normal microbiome of the stomach [possibly 100 bacterial species] may influence *H. pylori*-associated gastric pathogenesis by modulating inflammatory responses [38].

It has been estimated that about 10% of patients with *H. pylori* infection/colonization develop severe gastric lesions such as peptic ulcer disease and 1–3% progress to carcinoma. The model for gastric cancer development proposed by Correa et al. [39] in 1975 is still applicable presently: initial chronic gastritis or changes in the first decade of life [which is now known to be from *H. pylori* infection], result in atrophic gastritis progressing to intestinal metaplasia, then dysplasia with development of cancer over the next 30–50 years. The model for gastric cancer is similar for other inflammation-associated cancers. The evidence for *H. pylori* cancer connection is based on three large nested case control studies with follow-up for about 10 years, and meta-analysis of these studies reported an odds ratio of 3.8

[95% confidence interval {CI}, 2.3–6.2] with *H. pylori* infected versus uninfected persons [40]. The World Health Organization [WHO] subsequently declared *H. pylori* as a definite [group 1] carcinogen, responsible for about 90% of the global burden of noncardia gastric cancer [41]. CagA-positive *H. pylori* [more common strains worldwide] increase the risk of cancer to a greater extent than the rare CagA-negative strains, and in vitro CagA protein has oncogenic properties [41]. The molecular basis for cancer transformation is more complex and may include *H. pylori*-induced DNA damage. The bacteria causes characteristic DNA damage pattern in human cells, which can be correlated with chromosomal changes in gastric cancer [42, 43]. Epigenetic mechanisms associated with DNA methylation to regulate gene expression may be *H. pylori*-induced and this could cause silencing of several tumor-suppressive genes [44]. The mechanism for cancer development involves a distorted balance between cell survival and physiological cell death. *H. pylori* induce a major cell survival factor [NF-kB] and affect the apoptotic pathways of gastric epithelial cells [45].

The outcome of *H. pylori* infection is determined by bacterial, host genetic, and environmental factors, including the gut microbiome. This is reflected by the fact that most persons with chronic lifelong infection never develop any clinical illness. The majority of *H. pylori*-associated gastric cancer occurs in Southeast Asia, partly because of greater prevalence of infection, earlier age of acquisition, possibly more virulent strains, and genetic predisposition. Many studies have reported genomic markers, single nucleotide polymorphisms [SNPs], linked to *H. pylori* infection and gastric cancer [46]. Meta-analysis of 37 studies implicate IL-β 31 C > T polymorphism has increased risk for gastric cancer with *H. pylori* infection [47]. Il-10 [-592C>] promoter polymorphism is also associated with gastric cancer in Asians [48]. Other studies showed that specific Toll-like receptor [TLR]-1 and TLR-10 polymorphisms contribute to increased susceptibility [45]. In another meta-analysis of a group of polymorphisms in inflammation-related genes, encoding proteins of IL-1β, interleukin antagonist receptor, IL-8, IL-10, and TNF-α, Il-antagonist receptor 2 polymorphism was found to increase the risk of gastric cancer in non-Asian populations [49]. Animal models of gastric cancer and *H. pylori* infection, using genetically modified mice, have also shown a complex relationship with genetic background, gender, diet, inflammatory cytokine pathways, and the gut microbiota in the pathogenesis of these cancers [50].

Gastric extranodal MALT lymphomas are strongly associated with *H. pylori* infection or colonization. In a previous review of this condition, 79% of 1844 cases of MALT lymphoma were associated with *H. pylori* infection [51]. These neoplasms are B cell lymphomas that develop within the mucosa-associated lymphoid tissue of the stomach. In the USA, the incidence of MALT lymphomas between 2001 and 2009 was estimated to be 3.8 in 1,000,000 people, a rare complication of *H. pylori* infection [52]. Chronic inflammation [chronic gastritis] is the key basic mechanism predisposing to gastric cancer and MALT lymphoma but it is unclear why some patients develop one form of neoplasm instead of the other. Like gastric cancer, CagA plays a major role in the pathogenesis and the direct role of *H. pylori* is evident by the detection of lymphoma B cell clone in the chronic gastritis that preceded the

lymphoma [53]. Characteristic cytogenetic profiles have been described for MALT lymphoma and the formation of MALT1–AP12 fusion oncogene by the t [11:18] translocation is an important factor [54]. Expression of AP12 [encoding the cellular inhibitor of apoptosis 2] is under control of the MALT1 promoter. MALT1 encodes mucosa-associated lymphoid tissue lymphoma translocation protein 1, which is essential for the activation and proliferation of T- and B lymphocytes and NF-kB activation [54]. *H. pylori* also induce NF-kB expression [45].

4.5 Treatment of Clinical Diseases Associated with *H. pylori* Infection

Diagnostic tests for *H. pylori* are indicated for patients with symptoms suggestive of peptic ulcer, past peptic ulcer disease not treated with antibiotics, evidence of low-grade gastric MALT lymphoma, those with endoscopic resection of gastric cancer, and consider in patients under 55-years old with persistent uninvestigated dyspepsia and subjects with strong family history of gastric cancer. The diagnostic tests available for *H. pylori* include antibody tests, urea breath tests, stool antigen tests, and endoscopic biopsies [55]; see Table 4.1. *H. pylori* serology is useful for diagnosing infection but is not very good for test of cure or presence of active infection as the antibodies can persist years after eradication [55]. The urea breath test is accurate to determine active infection as it becomes negative shortly after eradication. Endoscopy is accurate to diagnose ulcers, inflammation, MALT lymphoma, and gastric cancer and the presence of *H. pylori* by urease test, PCR or culture. Stool antigen detection can also be used for evidence of eradication and presence of active infection and is the most cost-effective test.

Table 4.1 Diagnostic tests for *H. pylori* infection

Type	Accuracy	Availability	Utility for eradication
Serology [ELISA/IgG—inexpensive]	>85%	Readily available	Poor—decrease titer in 3–6 months
Urea breath test (nonradioactive or radioactive 14C—relatively expensive)	88–95%	Limited—variable	Very good
Endoscopic biopsy (urease test, Giemsa, or specific immune stain—expensive)	>90–95%	Invasive/GI consult	Invasive and inconvenient
Stool antigen (monoclonal enzyme immunoassay—very cost-effective, not readily available)	94–97%	Limited, underused	Very good, 4-weeks post treatment

Reference: Crowe S. Indication and diagnostic tests for *Helicobacter pylori* infection. UpToDate. www.uptodate.com 2017
Availability data based on Canadian experience

4.5.1 Peptic Ulcer Disease

It is estimated that 10% of people with dyspeptic symptoms have peptic ulcer disease and 95% of duodenal ulcers and 70% of gastric ulcers are associated with *H. pylori.* Older studies had demonstrated that antibiotic treatment to eradicate *H. pylori* [in absence of acid suppression] heal duodenal ulcer at a similar rate as acid suppression, but long-term ulcer relapse was markedly reduced but not completely eliminated with antimicrobial therapy and short-term acid suppression [56]. Initially two antimicrobials and acid suppressant were used for 7 days, but increasing antibiotic resistance of the bacteria has resulted in the evolution of treatment to 14 days or sequential therapy or different antimicrobial combination or quadruple therapy with bismuth. In a recent systematic review of Cochrane Database, the result of treatment for *H. pylori* in peptic ulcer disease did not appear to be very dramatic. A total of 55 trials were reviewed, 34 of which assessed duodenal ulcer healing with *H. pylori* eradication therapy [3910 participants] plus short-term ulcer healing drugs [UHD], usually proton pump inhibitor [PPI]. The adjusted proportion of patients with ulcer persisting was superior with eradication therapy and UHD versus UHD alone, 12.4% versus 18.7% [57]. For duodenal ulcer recurrence, 12.9% with eradication therapy versus 64.4% with no treatment [very low quality evidence]. In gastric ulcer healing [1974 participants], eradication therapy and UHD resulted in 16.0% with ulcer persisting versus 13.0% with UHD. However, eradication was superior to no treatment in preventing gastric ulcer recurrence, 16.3% versus 52.4% [57]. The authors of the review concluded: there is no evidence that *H. pylori* eradication therapy is an effective treatment for gastric ulcer or that it is more effective in preventing recurrence of duodenal ulcer compared to UHD. Thus, the principal benefit of antibiotic therapy is the prevention of recurrence when short courses of UHD is used, 80% risk reduction of duodenal ulcer and 69% for gastric ulcer. Randomized trials have shown that treatment of *H. pylori* infection in subjects starting long-term NSAID therapy reduces the risk for peptic ulcer disease [58].

The primary predictor of *H. pylori* eradication success is antibiotic resistance. The prevalence of antibiotic resistance is regionally variable and has been increasing in many countries; hence, eradication rate *of H. pylori* has been declining globally. Clarithromycin resistance has been rapidly increasing in many countries over the past decade; with rates of 30% in Japan and Italy, 50% in China, and 40% in Turkey [59]. Clarithromycin resistance has remained low in some European countries with low prevalence of *H. pylori* infection, such as Sweden [below 5%]; but widespread use of macrolides in children appears to be fueling resistance in the pediatric population in the USA, with up to 50% resistance reported [60]. There is also a trend to increasing levofloxacin resistance with over 20% in Europe to 34.5% in China [59]. In US veterans, *H. pylori* cultured from 135 patients revealed only 48.2% were susceptible to all five antibiotics tested [61]. Resistance prevalence was 31.3% to levofloxacin, 20.3% to metronidazole, 16.4% but later 24.2% to clarithromycin, 0.8% to tetracycline, and 0% to amoxicillin. Of seven strains from women resistant to clarithromycin, levofloxacin, and metronidazole were over 40% [60].

Tetracycline resistance has been reported to be low in Europe and Hong Kong [05–0.7%] and absent in most countries; but amoxicillin resistance is much more variable—0 < 2% in European countries, with up to 38% in Asia and South America [59]. In vitro resistance to amoxicillin may not reduce treatment efficacy [62]. Metronidazole resistance has been increasing in many countries worldwide, 20–40% in Europe and the USA, 50–80% in developing countries, 18–22% in Canada, and 9–12% in Japan [59].

4.5.2 Dyspepsia

Dyspepsia [discomfort or pain in the upper abdomen, not due to peptic ulcer, biliary or pancreatic disorders] is very common globally with prevalence of up to 20% in the population [63]. Most patients with dyspepsia have no organic disease and the majority appears to suffer from a functional disorder. However, patients' ≥60 years of age or family history of gastric carcinoma should undergo an endoscopy to exclude neoplasm [64]. Women, smokers, and users of nonsteroidal anti-inflammatory drugs [NSAIDs] have increased prevalence and dyspepsia maybe medication induced. Based on therapeutic trials, it is estimated that 10% of dyspepsia is due to *H. pylori* infection [probably acute].

In a randomized study published in 2010, 1517 *H. pylori* positive adults with dyspepsia were treated with antibiotics or placebo and followed prospectively [63]. Among the treated group [90% eradication], there was a small but significant reduction in subsequent symptoms. A recent review and meta-analysis of 23 randomized controlled trials [RCTs] with several thousand patients have been published [65]. The results of the review are mixed and the overall benefit of treatment appears to be very questionable. Eradication of *H. pylori* did not result in clinical improvement during short-term follow-up of <1 year but inexplicably symptom improved after a year. Six studies showed that eradication therapy did not improve the quality of life and there were increased treatment-related side effects in 10 studies. Ten studies showed eradication therapy caused resolution of chronic gastritis on histology [65]. However, despite lack of good data and controversy, clinical guidelines recommend that eradication therapy should be offered to patients with *H. pylori* infection [64].

4.5.3 MALT Lymphoma

MALT lymphoma [MALToma] is also labeled as marginal zone B cell lymphoma of MALT type, represents a group of lymphomas originating from B lymphocytes of the "marginal zone," which is the external part of the secondary lymphoid follicles, but is extranodal [66]. The other types of marginal zone lymphoma can be splenic or nodal and MALToma is the commonest type of this group, accounting for 5–8% of all B cell lymphomas and has been described in nearly all tissues.

MALTomas arise from lymphoid populations that are induced by chronic inflammation in extranodal sites. Gastric MALToma is the most frequently recognized and is incontestable associated with chronic gastritis induced by *H. pylori*, but other microbes are associated with MALT lymphomas at other anatomical sites [66]. Besides infection, MALT lymphomas can be induced by other chronic inflammatory disorders caused by autoimmune disturbance, such as Hashimoto thyroiditis and Sjogren syndrome.

It is generally recommended by guidelines that localized gastric MALToma should be treated with antibiotics to eradicate *H. pylori* as the sole first-line therapy. This is based on retrospective and prospective observational studies but no randomized controlled trial. In a previous review of prospective cohort treatment studies [in 2009] of localized MALTomas, tumor regression was reported to occur in 60–93% [67]. However, treatment response was variable with some patients showing delayed response and others relapse within a year. In a long-term, multicenter cohort of 420 Japanese patients treated for *H. pylori*, 77% showed resolution or minimal residual disease on histology but 10 [3%] responders relapsed in 6.5 years [68]. Among 120 German patients followed for 10 years, eradication therapy resulted in remission in 80% with 3% recurrence within 24 months and another 17% had histological evidence of residual disease at 48 months [69]. There is also evidence that limited stage diffuse large B cell lymphoma [normally treated with cancer chemotherapy] can respond to antibiotic eradication therapy [70]. A phase 2 multicenter study showed that exclusive antibiotic *H. pylori* eradication therapy resulted in complete remission in 63% [71].

4.5.4 Gastric Cancer

The treatment for early gastric cancer is surgical excision but there is evidence that *H. pylori* eradication in infected patients can prevent recurrence. Endoscopic resection has now become standard therapy for localized early gastric cancer but recurrence in the remnant stomach is higher than gastrectomy. The incidence of metachronous recurrent gastric cancer after endoscopic resection after 3–5 years is 2.7–14.0%; and eradication therapy showed reduction of recurrent cancer by about 54–60% in two recent meta-analyses [72, 73]. In a recent prospective, double-blind, placebo-controlled trial of 470 patients with early gastric cancer or high-grade adenoma from South Korea, after endoscopic resection antibiotic eradication therapy or placebo was administered. After a median of 5.9 years metachronous gastric cancer developed in 7.2% of the treated group compared to 13.4% [almost 50% reduction] in the placebo group, $p = 0.03$ [74].

Initial epidemiological studies on the risk of stomach cancer and *H. pylori* infection had focused on distal non-cardia gastric cancers, but recent studies have found that the infection is the principal risk factor for all gastric adenocarcinoma [75, 76]. There are proponents for mass *H. pylori* eradication therapy for people with asymptomatic infection to prevent development of gastric cancer but the beneficial effect

on different populations remains unclear. The incidence and risk of stomach cancer varies widely across regions and populations, depending on the prevalence/incidence of *H. pylori* infection, age of onset, genetic background, probably virulence of the strain, environmental factors, and likely the microbiome of the host. Initial trial in China, with high incidence of *H. pylori* and gastric cancer, of 1630 healthy carriers randomized to 2-week course of eradication therapy versus placebo showed after 7.5 years similar risk of gastric cancer in the population, but decreased stomach cancer in the subgroup without precancerous lesions [gastric atrophy, intestinal metaplasia, or gastric dysplasia [77]]. In a larger trial [$n = 3365$] with 14.7 years follow-up [also in China], *H. pylori* eradication therapy reduced the risk of gastric cancer by 39%, 3.0% in the treated group versus 4.6% in the control group [odds ratio [OR] = 0.61, $p = 0.32$] [78]. Also, a study from Taiwan found eradication treatment reduced the severity or reverse the presence of atrophic gastritis and premalignant gastric lesions [79]. A large observational study from Hong Kong of 73,237 subjects treated for *H. pylori* compared with the matched general population, found significant lower risk of gastric cancer, particularly in those ≥60 year of age, ≥10 years after treatment [80].

In a previous review and meta-analysis of six RCTs published in 2014, eradication therapy resulted in about 33% reduction of gastric cancer—1.6% in the treated group versus 2.4% in the control group [81]. It was estimated that the number to treat to prevent one stomach cancer was as low as 15 Chinese men and as high as 245 American women. A more recent review and meta-analysis assessed 24 studies [RCTs and cohort studies] with 715 incident gastric cancers in 48,064 individuals followed for 340,255 person-years [73]. Only two of the studies were conducted in regions outside of Asia [Columbia and Finland]; the baseline incidence of stomach cancer varied from 29.0 [Finland] to 469.0 per 100,000 person-years in studies for primary prevention. In regions with intermediate and the highest tertiles of baseline gastric cancer incidence, eradication therapy reduced gastric cancer compared to no treatment; the pooled incidence rate ratios were 0.49 and 0.45, respectively. But the benefit of treatment was not significant for regions of the lowest tertile for gastric cancer, pooled incidence rate ratio was 0.80 [73]. *H. pylori* eradication therapy also reduced gastric cancer in high-risk individuals with atrophic gastritis and intestinal metaplasia.

4.5.5 Miscellaneous Conditions

H. pylori infection is associated with iron deficiency of unexplained cause in adults and children [82]. An acidic environment facilitates dietary iron absorption and atrophic gastritis with hypochlorhydria may predispose to iron deficiency. Recent reviews and meta-analysis have concluded that *H. pylori* eradication treatment improves unexplained iron deficiency anemia [83, 84], and this has been recommended by guidelines in patients with normal upper and lower gastrointestinal

endoscopies [85]. Chronic infection with atrophic gastritis can also lead to impaired vitamin B12 absorption and increased serum homocysteine [86].

Idiopathic thrombocytopenia purpura [ITP] is also associated with *H. pylori* infection and development of atrophic gastritis [87]. Guidelines on ITP recommend testing for *H. pylori* and treat with eradication therapy if infection is present [88, 89]. The prevalence of *H. pylori* infection in ITP reflects the variation in prevalence of the population in the geographic region, higher in developing countries compared to developed nations. The mechanism or pathogenesis of *H. pylori*–ITP is unclear, but eradication therapy has been associated with resolution of ITP in about half of eradicated adult patients [90]. Data in children of *H. pylori*–ITP has been limited but in a cohort of 244 children with ITP in Italy, 20% had *H. pylori* infection [91]. Eradication was successful in 33/37 treated patients [89%] and of these 39% had resolution of ITP compared to 10% spontaneous remission in noninfected children [$p < 0.005$]. Table 4.2 summarizes the indications for *H. pylori* treatment.

4.6 Treatment Regimens for *H. pylori* Infection

Triple therapy containing clarithromycin, amoxicillin, or metronidazole with a PPI for 7–14 days has been the most common first-line therapy for *H. pylori* infection. However, with the rate of increasing clarithromycin resistance, this triple regimen has resulted in eradication rates of less than 80% in many developing countries, especially in Asia [92]. Controlled, randomized trials from North America since 2000 had also shown eradication rates below 80% with this triple regimen for 7–10 days [93]. Limited data from North America and meta-analysis of the world's literature indicate that clarithromycin triple therapy, when indicated, should be used for 14 days as it is more effective than 7–10 days treatment [93]. This regimen is not recommended for regions with clarithromycin resistance >15% or patients with

Table 4.2 Indications for *H. pylori* treatment

Conditions	Guidelines	Comments	Viewpoint
1. Peptic ulcer disease	Recommended	Clear cut	Agree
2. Early gastric MALToma	Recommended	Treatment of choice	Acceptable
3. Localized gastric cancer	Recommended	Post-resection	Acceptable
4. Dyspepsia	Trial recommended	Questionable data	Would not recommend
4. Iron deficiency of no cause	Recommended	Observational data	Reasonable/limited data
5. Immune ITP	Recommended	Observational data	Reasonable/limited data
6. Asymptomatic [prevention]	Consider	High-risk countries of gastric cancer	? Family history of gastric cancer [not studied]

previous macrolide exposure for any reason [94, 95], as a meta-analysis found eradication rate of 22% for clarithromycin-resistant *H. pylori* strains compared to 90% for sensitive strains [96]. There is no large-scale data on clarithromycin resistance of *H. pylori* strains in North America and Europe, but recent data from veterans in Houston indicate resistance rates are >15 to 20% [60].

It has been recommended that bismuth quadruple therapy [bismuth, metronidazole, tetracycline, and PPI] for 10–14 days should be used as first-line therapy in areas of high clarithromycin resistance, as the efficacy is not affected by clarithromycin resistance and is less affected by metronidazole resistance [94]. Even in areas of high metronidazole resistance, bismuth quadruple therapy [BQT] for 10–14 days achieved >85% eradication rate [97]. Although a single large trial showed no difference in eradication rate between 10 and 14 days treatment [91.6–92.6%] [98], some studies indicate that a 14-day course of BQT is preferable in areas with high metronidazole resistance [99, 100]. Tolerability and pill burden of the BQT maybe improved with a triple-drug capsule [containing bismuth, metronidazole, and tetracycline] plus a PPI, with eradication rates >90% even for cases of rescue therapy after failure of standard triple therapy [101, 102].

Concomitant therapy [non-BQT] consists of PPI, amoxicillin, clarithromycin, and metronidazole or tinidazole for 5–14 days has been assessed in various studies and is a preferred non-bismuth therapy. Compared to standard triple therapy for the same duration the rates of eradication are similar. Several RCTs and review of multiple studies suggest that longer duration is more effective [103] and the ACG guideline recommend 10–14 days [94] but the European guideline prefers 14 days [95]. High prevalence of *H. pylori*-resistant strains to clarithromycin and metronidazole can result in decreased response even with 14-days course, as reflected by 75% and 80.8% eradication in Turkey and South Korea [104, 105]. An "optimized" concomitant regimen [new generation PPI with higher dose, esomeprazole 40 mg twice daily] for 14 days demonstrated higher eradication rates of 91% versus 86% with standard concomitant regimen [106].

Sequential therapy, as an alternative to triple therapy, was introduced in 2000, consisting of PPI plus amoxicillin for 5 days, clarithromycin and metronidazole [or tinidazole] for another 5 days. Multiple comparative RCTs have been performed with geographical variation in efficacy, which likely reflect variation in clarithromycin resistance. In a systematic review and meta-analysis of 46 RCTs with >13,500 patients, the overall eradication rate of sequential therapy was 84.3%, superior to 7 days clarithromycin triple therapy but equivalent to 14 days triple therapy or 10–14 days of BQT [107]. Comparative studies and overall review of the literature indicate that sequential therapy is less effective than concomitant therapy against clarithromycin-resistant strains and for similar duration of treatment [95].

Hybrid therapy represents a cross between sequential and concomitant therapy, consisting of PPI and amoxicillin for 7 days followed by another week of PPI, amoxicillin, clarithromycin, and metronidazole or tinidazole [108]. The overall efficacy is about 88% but there is no significant difference in the tolerability, efficacy, or compliance observed with hybrid, sequential, or concomitant therapies [93].

Less data is available for second-line therapies for treatment failures, using levofloxacin or rifabutin in triple or quadruple concomitant or sequential regimens. Rising quinolone resistance in many areas of the world has compromised levofloxacin response and rifabutin-containing regimens maybe a better option for rescue therapy [95]. Levofloxacin-resistant strains in North America may be as high [or greater] than clarithromycin resistance [93]. Bismuth–levofloxacin quadruple therapy appears to be effective for second- or third-line therapy for 10–14 days based on limited data [96].

Adjunctive therapy with probiotics for *H. pylori* infection is gaining international attention. There is emerging evidence that some *Lactobacillus* and *Bifidobacterium s*pecies can inhibit *H. pylori* and reduce the bacterial density on gastric mucosa and improve histopathological features of damage and inflammation [109]. This is important as increased density of *H. pylori* on the gastric mucosa is linked to more severe gastritis and increased incidence of peptic ulcer, atrophic gastritis, and probably gastric cancer. Clinical studies indicate that probiotics added to standard regimens improve eradication by 10%, with greater symptoms relief and less side effects [109]. A meta-analysis of 10 clinical trials [mainly from China] with adjuvant probiotics showed increased cure rates and less side effects of treatment [110]. A more recent review and meta-analysis of 45 RCTS with 6997 participants confirmed these results, with eradication rates of 82.3% and reduced side effects with probiotics compared to 72.1% without probiotics [111]. There are several limitations of the probiotic supplementation trials such as various types of microbes, differences in doses and duration. Thus, standardization of the components, dose, and duration are needed, with additional large multiregional, randomized trials before universal adaption.

With the various regimens available for *H. pylori* infection, it can be confusing for the clinicians to choose the most appropriate therapy; Table 4.2 summarizes the main therapeutic regimens. A recent comprehensive systematic review and meta-analysis attempted to determine the most effective treatment with the lowest risk of adverse events [92]. The analysis included 143 studies with 14 kinds of treatment with data from 32,056 patients, using intention to treat analysis. With respect to duration of treatment, longer treatment courses overall were better, including standard triple therapy, levofloxacin-based triple treatment, probiotic-supplemented triple regimen, and bismuth-based quadruple therapy [92]. The previously recommended 7 days standard triple therapy was the least effective. No single regimen was considered superior but the best choices for eradication of *H. pylori* include 10–14 days of concomitant treatments, probiotic-supplemented triple regimen, levofloxacin-based triple treatment, bismuth-based quadruple regimen, sequential treatment, and 14 days of hybrid therapy. Adding probiotics appears to enhance tolerance and efficacy of the triple regimens. To resolve the problem of choosing an appropriate regimen, a treatment algorithm could be used based on Table 4.2, partly based on ACG and European guidelines [93, 95].

In a recent large prospective controlled trial in rural China for gastric cancer prevention, 10 days BQT resulted in *H. pylori* eradication in only 73% and 15% in the controlled group, omeprazole, bismuth, and placebo antibiotic [112]. The risk

Table 4.3 Main regimens for *H. pylori* infection

(a) Industrialized countries with low macrolide resistance [<15%]
First-line–Standard triple drugs × 14 days
PPI [standard or double dose], clarithromycin 500 mg, amoxicillin 1 g—all BID, in penicillin allergy metronidazole 500 mg TID
(b) Developing countries and others with high macrolide resistance [>15%]
First-line—Bismuth quadruple therapy × 14 days plus possible probiotics
PPI [standard dose] BID, bismuth subcitrate [120–300 mg] or subsalicylate [300 mg] QI
Tetracycline 500 mg QID, metronidazole 250 mg QID, or 500 mg TID
Probiotics*: Lactobacillus* and *Bifidobacterium* strains with >1 × $10^{7–9}$ cfu/mL per strain
(c) Second-line therapies:
(1) Failure of standard triple drugs (a)—Best choice bismuth quadruple therapy plus possible probiotics (b)
(2) Failure of bismuth quadruple drugs—best choices: Levofloxacin triple therapy for 14 days [PPI BID, levofloxacin 500 mg OD, amoxicillin 1 g BID × 14 days]; or levofloxacin sequential therapy [PPI double dose and amoxicillin 1 g BID for 7 days, then PPI, amoxicillin, levofloxacin 500 mg OD, and metronidazole 500 mg BID × 7 days
(3) promising salvage therapy: LOAD—PPI [double dose] QD, levofloxacin 250 mg QD, nitazoxanide 500 mg BID, and tetracycline 500 mg QID × 10 days [expensive and needs further study]
Or levofloxacin, rifabutin, and rabeprazole

BID twice daily, *QD* once daily, *QID* four times daily, *TID* three times daily, *cfu* colony forming units

factors for eradication failure were missed medication doses, male sex, smoking, alcohol consumption, history of stomach disease, and higher body mass index. This raises the issue of personalized treatment, such as longer course and higher dose of new PPI for patients with multiple risk factors for eradication failure (Table 4.3).

4.7 Prevention of *H. pylori* Infection

Based on the global epidemiology of *H. pylori* and patterns of regional distribution, it appears that prevention in high prevalence countries could be partly achieved by improvement in sanitary and socioeconomic conditions. However, this has remained unachievable in many low-middle income countries with overpopulation. An effective *H. pylori* vaccine is feasible based on animal experiments and human trials [phase 1–3] have been performed in China for over a decade. An oral recombinant *H. pylori* vaccine using urease B subunit fused with heat-labile enterotoxin B subunit [*Escherichia coli*] was developed in China. A phase 3 trial was conducted in Ganyu County, Jiangsu Province, China in 4464 children, aged 6–15 years, with no previous *H. pylori* infection and given three-dose oral vaccine or placebo, and followed for 3 years for safety and acquisition of *H. pylori* infection [113]. The vaccine was found to be safe and immunogenic with a protective efficacy of 71.8%.

Widespread use of this vaccine globally may be a problem until further refinements are made. The challenges of global marketing of this vaccine [discussed in the accompanying editorial] include (1) administration barrier, the need for 2 h fasting and a bicarbonate solution [for stomach acid buffering] before the vaccine; (2) the potential rare severe side-effects from the heat-labile toxin, but not reported in this study; and (3) the waning immunity after a year of the vaccine, suggest the need for a booster dose [114]. Whether the vaccine has any therapeutic value may be considered in future trials.

4.8 Comments and Future Directions

Treatment for *H. pylori* is clearly indicated for infected patients with peptic ulcer disease, early stage MALT of the stomach, resected early gastric cancer, and for asymptomatic Asians from areas with high endemic rates of gastric cancer, such as China. International studies are needed in low prevalence countries to assess benefit of preventive therapy in asymptomatic infection with family history of stomach cancer. It may be considered but not well established for infected patients with iron deficiency of unknown cause and ITP. In view of the global increase of antimicrobial resistance in general, it is my opinion that *H. pylori* eradication therapy should not be used for dyspepsia, largely a functional disturbance. The presence of *H. pylori in dyspepsia* could be incidental or be secondary to acute infection, in which case symptoms are usually short lived. In my opinion, screening and treating subjects starting long-term NSAIDS should not be routinely done, as this is a large population of individuals which would result in further overuse of antibiotics resulting in worsening of the "global crisis" of antibiotic resistance. Recently, a systematic review of the global antibiotic resistance in *H. pylori* from 65 countries have highlighted the worsening trend: primary and secondary resistance rates to clarithromycin, metronidazole and levofloxacin were ≥15% in all regions, except primary clarithromycin resistance in the Americas [10%] and Southeast Asia [10%] and primary levofloxacin in the European region [11%] [115].

Subjects with asymptomatic infection in developed countries [low prevalence of *H. pylori* infection and gastric cancer] should not be treated, although it may be considered for subjects with a family history of gastric cancer or if genetic studies demonstrate at risk polymorphisms. Can *H. pylori* infection be beneficial to the host? There is some evidence that *H. pylori* infection is associated with decreased risk of GERD [4], possibly through chronic gastric atrophy and hypochlorhydria. There is also evidence that childhood *H. pylori* infection protects against the development of asthma and allergic disorders [116].

Future placebo-controlled, randomized larger trials are needed to prove the benefit of *H. pylori* eradication therapy for iron deficiency of unknown cause and ITP. Standard triple therapy [commonly in industrialized countries] should be studied with and without a standard high dose probiotic [with *Lactobacillus* and *Bifidobacterium* species used in Asian studies] in RCTs in Europe and North

America. Another larger and longer vaccine trial should be performed, in multiple countries with high rates of gastric cancer and *H. pylori* infection. Reformulation of the vaccine for simplification of administration should be investigated and implemented before the next large trial.

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Chapter 5
Major Advances in Hepatitis C Treatment but Not Hepatitis B

5.1 Introduction

Chronic hepatitis B and hepatitis C infection are prevalent worldwide and are estimated to affect over 500 million people globally. Both pathogens can produce acute and chronic hepatitis, prolonged subclinical infection with liver fibrosis leading to cirrhosis, and ultimately liver failure and hepatocellular carcinoma (HCC) and death. Global deaths from viral hepatitis have increased by 63% from 0.89 million in 1990 to 1.45 million in 2013, and disability increased 34%, from 31.7 million to 42.5 million, attributable mainly to hepatitis B and C, 96% of deaths and 91% of disability [1]. The absolute increases in morbidity and disability could be accounted for by the population growth. Since the discovery of the hepatitis B virus (HBV) in 1965 significant progress has been made in prevention, with the first commercial vaccine introduced in 1981 (Heptavax) which was subsequently replaced by DNA recombinant vaccines in 1986 [2], and later antiviral drugs to control chronic infection but rarely produced cure were marketed in the late 1990s. Currently it is estimated that >350 million people have chronic hepatitis B virus (CHB) infection, predominantly in Asia and sub-Saharan Africa [3], and 2.2 million people are chronically infected in the USA, of whom 1.3 million (60%) are foreign-born [4].

Hepatitis C virus (HCV) is estimated to infect 170 million people worldwide [5], including 2.7–3.9 million living in the USA [6]. Infection with the virus becomes chronic in 75–85% of HCV-infected persons, but greater in those with subclinical acute infection compared to subjects with acute hepatitis syndrome. Chronic HCV infection result in severe complications in 10–20% of patients and it is the main cause of cirrhosis, HCC, and liver transplantation in the USA and leads to 15,000 deaths annually [7]. The progress and advances in HCV science since its discovery within the last 30 years are astronomical and unprecedented in medical science: defining the agent, understanding the biology, and developing safe and

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effective antiviral agents that can produce cure in most patients with relatively short treatment course.

5.2 Background and Natural History

5.2.1 Hepatitis B Virus

The highest burden of CHB is in Asia and Africa where transmission is mainly vertical from mother to child and >90% of infected subjects become persistent or chronic carriers [8]. In industrialized countries transmission of HBV is mainly horizontal in adults via sexual contact or percutaneous/parenteral exposure, and clearance of the virus occurs in 95% of immunocompetent persons but 5% develop chronic infection. Although the current paradigm is that patients with anti-HBV surface antibodies (anti-HBs) have cleared the virus, there are a couple of studies on a few patients which showed persistence of the virus or histological abnormalities after presumed clearance of the virus. One study found HBV DNA in the liver in 13 of 14 healthy liver transplant donors who were positive for anti-HBs and anti-HBc [9]. In another series persistent liver fibrosis and mild inflammation were present in nine patients up to 10 years after serological recovery of acute infection [10]. Interpretation of these observations is difficult due to the limited number of subject studied but suggests that complete eradication of HBV may not occur after recovery from acute infection and development of anti-HBs.

The natural history CHB infection has been described in four phases (see Fig. 5.1), which is a reflection of viral replication and the host immune response. Not everyone with chronic infection goes through all phases, which are of variable duration. (1) The immune-tolerant phase, occurs in infants with perinatal infection due to the immature immune system, and characterized by high levels of HBV DNA and consistently normal alanine aminotransferase (ALT) levels. Liver biopsies reveal absence of inflammation or fibrosis. This phase usually occurs in the first 2–3 decades of life and although there is immune tolerance the T cell function is preserved [11]. In adults with HBV infection by horizontal transmission there is no immune-tolerant phase. Perinatal infected individuals usually enter the immune clearance phase by the third to fifth decades of life (median age 30 years). (2) The immune-active phase is characterized by increased ALT levels and HBV DNA with liver inflammation and injury. The outcome of this phase is variable. Some patients accomplish HBeAg seroconversion and HBV DNA suppression to transition to the inactive chronic HBsAg carrier phase with usually good prognosis. Others fail to control the virus and remain in the immune-active phase for many years, with cumulative liver injury, progressive liver fibrosis, and development of cirrhosis [12]. The rate of spontaneous seroconversion from $HBeAg^+$ to $HBeAg^-$ (development of anti-HBe) is less than 2% per year in children under 3 years of age and increases in puberty and young adulthood to 8% and 12% per year [13]. (3) The inactive chronic

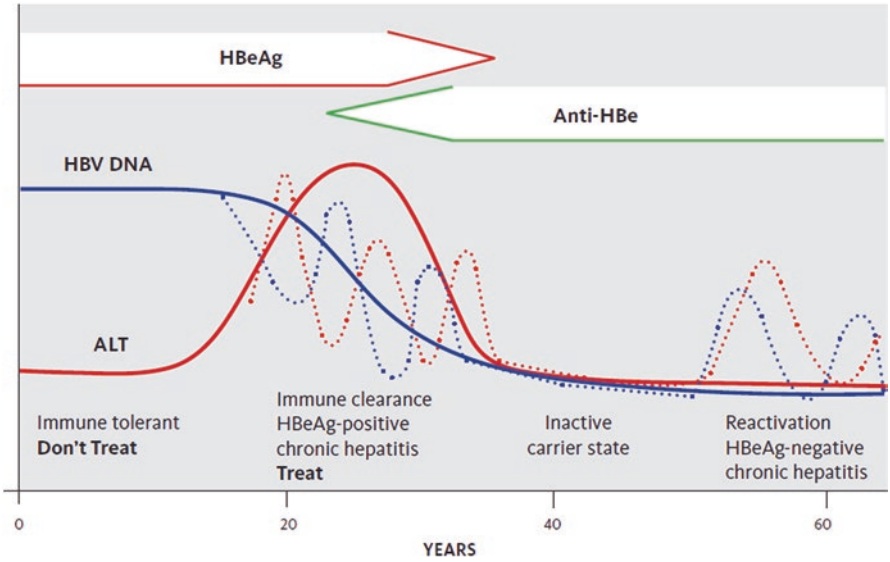

Fig. 5.1 Natural course of chronic HBV infection. The natural course of HBV infection is illustrated above but not all patients go through every phase, for example the immune tolerant phase is not usually present in adult acquired infection. Adopted from Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006; 43: S173

HBV phase after HBeAg seroconversion can continue and remain inactive in 67–80% of patients, with low or undetectable HBV DNA, normal ALT, and minimal liver necroinflammation [13]. Some inactive carriers (about 4–20%) have one or more reversions back to HBeAg-positive. (4) The immune reactivation phase may occur in 10–30% of patients who seroconvert from HBeAg-positive to HBeAg-negative state, with elevated ALT and high HBV DNA; and 10–20% of inactive carriers may have exacerbation of hepatitis with HBV replication after years of quiescence. Extrahepatic manifestations can be seen in 10–20%, mediated by circulating immune complexes, such as periarteritis nodosa and glomerulonephritis.

Resolution of CHB infection spontaneously or by treatment is defined by clearance of HBsAg and development of HBs-antibody and this may occur spontaneously in about 0.5% per year in patients with inactive chronic infection and up to 1.6% per year in HBeAg-negative persons [13]. A minority of these patients may have transiently detected low-level HBV DNA in serum [14]. Clearance of HBsAg rarely occurs with treatment and improves the prognosis, but occasionally HCC can occur in older patients when resolution occurred after development of cirrhosis or with HCV coinfection [15].

The risk of liver-related complications is very variable and related to age of onset, coinfection with human immunodeficiency virus (HIV), HCV, hepatitis D virus (HDV) and alcohol intake and viral factors. In a study from Taiwan, the cumulative 10-year risk of cirrhosis with CHB infection alone was 9% but with

HCV and HDV superinfection the rates increased to 48% and 21%, respectively [16]. Sustained high HBV DNA, elevated ALT, and persistent HbeAg status are major determinants of progression to cirrhosis, and these factors with development of cirrhosis with HBV DNA >2000 units are predictors of HCC risk [17–19]. Studies in Asia have also shown that genotype C is associated with more rapid progression to cirrhosis and HCC than genotype B [14]. In patients with cirrhosis, the 5-year cumulative risk of liver failure or decompensation is 20% and the risk of HCC is 2–5% [20, 21].

HDV coinfect about 5% of 240 million people with chronic HBV infection and the rate of infection varies with geographical region and the risk population. HDV is the smallest known human pathogenic virus or incomplete virus, as it uniquely requires HBV to complete the replication cycle, as the HBVs Ag within the HDV envelope is necessary for viral entry into newly infected hepatocytes [22]. There are eight genotypes of HDV: genotype 1 is ubiquitous; genotypes 2 and 4 are mainly in Asia, genotype mostly found in the Amazon basin; and genotypes 5–8 predominate in sub-Saharan Africa.

5.2.2 Hepatitis C Virus

HCV is transmitted primarily by percutaneous exposure to infected blood and there is no well-defined geographical variation in the burden of disease globally. Blood-borne transmission is mainly by injection drug use through sharing of needles, syringes, and other paraphernalia and less commonly by nosocomial exposure to infected blood. Sexual transmission can occur as the virus is found in semen but heterosexual transmission is inefficient and very rare [23]. However, sexual transmission among men who have sex with men (MSM), especially with HIV infection, is a significant risk with anal receptive sex and ejaculation without condom [24]. Rectal shedding of HCV has been detected in 47% of MSM and is associated with high blood viral load >5 $\log_{10}$ IU/ml [25]. Mother-to-child vertical transmission is less efficient than in HBV infection but occurs in about 4–5% [26] but not by breast-feeding.

Acute infection with HCV is largely asymptomatic or subclinical and only a small proportion of patients (15%) develop symptoms of mild–moderate acute hepatitis and fulminant hepatitis is extremely rare [27]. Spontaneous clearance of HCV usually occurs within 6 months but only in 15–45% (average 20%) and greater in symptomatic patients (40–52%), younger ages, women and persons with certain genetic polymorphisms [28]. Chronic HCV infection after acute infection is confirmed by persistent HCV RNA in blood after 6–12 months and most patients are asymptomatic. Occasionally patients may present with extrahepatic manifestations, such as cryoglobinemic vasculitis, kidney disease, porphyria cutanea tarda, non-Hodgkin lymphoma, and rheumatic symptoms [29]. The ALT may be intermittently or persistently elevated but can be consistently normal in about 20% of chronic HCV infection.

About 15–20% of chronic HCV-infected persons develop cirrhosis over 20 years but higher rate and more rapid progression can occur with coinfection with HBV and HIV, alcoholic abuse, and fatty liver. The course of liver fibrosis is similar among the six genotypes but genotype 3 is more commonly associated with liver steatosis [30]. Although the natural course of HCV infection varies, the best predictor of disease progression is the degree of hepatic fibrosis. In patients with minimal or no fibrosis and inflammation the risk of progression to cirrhosis in 10–20 years is very low. Once cirrhosis occurs the risk of HCC is as high as 3% per year without treatment and hepatic failure or decompensation becomes a concern.

5.3 Biology and Virology

HBV and HCV are both hepatotropic viruses that cause similar diseases of the liver but are from different viral families. HBV is a DNA virus (partially double-stranded) that replicates by reverse transcriptase and is member of the *Hepadnaviridae*, while HCV is a positive-strand RNA virus of the *Flavviridae* family, genus *Hepacivirus* which shares similarities to human pegivirus (formerly GB virus C or hepatitis G virus) and human hepigevirus-1 [31]. Although, both viruses share some structural features (enveloped with capsids) they differ markedly in their genome organization, Fig. 5.2 [32].

During infection the HBV attaches to the hepatocyte by the surface antigen (via interaction with heparin sulfate proteoglycans and liver-specific receptor sodium/taurocholate cotransporter) and the virus is then internalized and uncoated, and the DNA genome is delivered to the nucleus as a relaxed circular DNA where it is repaired to form a covalently closed circular DNA (cccDNA) [32]. The supercoiled cccDNA persists in the hepatocyte nucleus to form a stable minichromosome (chromatinized episome that resembles the host chromatin), which utilizes the cellular transcription machinery to produce all viral RNAs for protein production and replication in the cytoplasm [33]. Reverse transcription of the pregenomic RNA results in new DNA nucleocapsids that can recycle back to the nucleus to amplify the pool of cccDNA, or acquire HBsAg-containing envelope and exported from the cells as progeny virions [32]. With viral replication there is secretion of high levels of HBeAg and HbsAg into the circulation. These antigens are important in the evasion of the host immune response, and HBeAg (a tolergen) plays a role in establishing chronic infection during vertical transmission [34].

HCV attaches to hepatocytes and enters the cell by a receptor-mediated process, the genome enters the cytoplasm where it is translated and viral proteins assemble to form replication complexes for genome replication [32]. Progeny positive RNA strand acquires an envelope to become encapsulated and leaves the cell as progeny virions. A major difference from HBV is that HCV replication does not involve a DNA intermediate, occurs entirely in the cytoplasm, and does not establish a persistent nuclear viral genome. HCV is much more genetically diverse than HBV, with six well-known genotypes [1–6] further divided into multiple subtypes, which differ

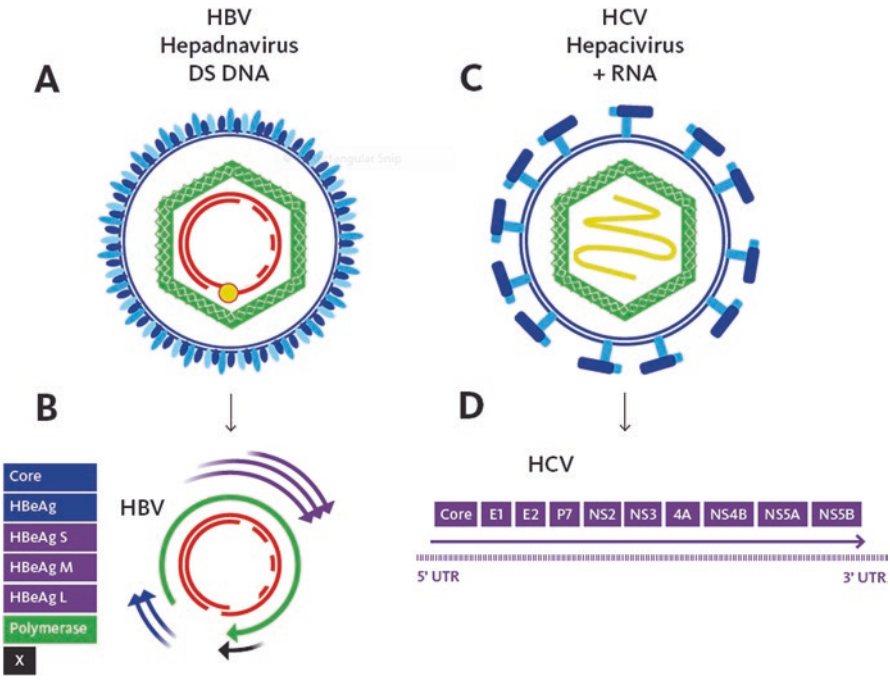

Fig. 5.2 Structure and genome organization of HBV and HCV. The structures of HBV and HCV have some similarities: both viruses are enveloped, with multiple surface proteins in the envelope, and each has a capsid made up of a single core protein; and some differences: HBV (42 nM) is smaller than HCV (50–60 nM), the HBV genome within the capsid is a double-stranded DNA and the HCV genome is a single strand of positive sense RNA. The genomic structures are differently organized: HBV has a compact genome organized in four overlapping or circular reading frames (ORFs): these include the surface antigen ORF (red), the core/precore ORF (blue) that form the HBcAg and HBeAg, the polymerase ORF (green), and the X ORF (black) that form the X protein; while the HCV genome is organized as a linear single polyprotein to give rise to ten viral proteins: structural protein core, envelope 1 (E1), envelope 2 (E2), nonstructural (NS) proteins, p7, NS2 protease, NS3/4 protease, NS4B, NS5A, and NS5B polymerase. Adopted from Delaney WE IV [31]

by 30% and 20%, respectively, at the nucleotide level. In 2006, a new HCV genotype was identified from patients in central Africa, genotype 7a and 7b [35], and most recently a novel genotype 8 was found in four patients from Punjab, India which was previously misidentified as genotype 5 [36]. Genotype 1 is the most frequent globally (46%), the most common in Europe, North America, and Australia; followed by genotype 3 (30%), mainly in South Asia; genotypes 2, 4, and 6 account for 23%; and genotypes 5 and 7 for <1% [36]. HBV has eight genotypes (A–H) which differ by about 8% at the nucleotide level [32], with similar clinical natural history and response to treatment. Compared to the HBV with circular genome and multiple overlapping reading frames, the HCV genome is organized in a linear manner which predisposes to greater number of viable mutations [32].

5.3.1 Impact of Genomic and Structural Differences on Antiviral Therapy

This topic was elegantly reviewed by Delaney [33] and will be summarized. Overall HBV has fewer viral targets for antiviral intervention than HCV. HBV has seven encoded proteins (some highly related) and only the polymerase has a classic enzymatic function, whereas HCV has ten distinct proteins with at least four recognized enzymatic functions (NS5B polymerase, NS3 helicase, NS2, and NS3/4 proteases).

The main therapeutic target of HBV is the polymerase enzyme which resulted in the development of five nucleoside/tide analogs, which require chronic dosing to suppress viremia but is usually ineffective in converting to HBs antigen-negative state. HBV replication is prone to error because of lack of proofreading activity of HBV polymerase, leading to emergence of viral variants which become resistant to the nucleos(tide) analogs. No other direct viral targets have been validated for therapy of HBV. Potential targets for drug development include HBcAg, viral RNAs, capsid, and viral entry. Experiments in cell culture and animal models have shown promise with small interfering (si)RNA with inhibition of one or more viral transcripts for prolonged periods [37, 38]. A novel therapeutic peptide (Myrcludex) that blocks viral entry in vitro and in animal models has completed phase 1 clinical study in healthy volunteers but it targets a host protein and not a viral protein [39].

Although all ten distinct proteins of HCV are potential therapeutic targets (especially several with enzymatic functions) drug development had focused on NS3 protease, the NS5A protein, and the NS5B polymerase.

5.3.2 Host–Viral Interactions

Both viruses use multiple mechanisms to evade the host immune surveillance system to avoid clearance. Impaired responses of either the innate immune system (first response) or the adaptive system (multi-epitope specific $CD4^+$ or $CD8^+$ T cell and B cell) responses can lead to failure of clearing primary infection with HBV or HCV). Dendritic cells (DC) and natural killer cells (NK) are essential components of the innate immunity in blood and the liver. DC initiates the primary immune response and coordinates the innate and adaptive immunity systems through stimulation of interferons (IFN)-α/β and ¥ and cytokines, which activate NK cells and $CD4^+$ and $CD8^+$ cell responses in HBV and HCV infection. NK cells increases by more than threefold in the liver compared to blood and can kill virus-infected hepatocytes by receptor-mediated lysis or by cytopathic mechanisms (granzyme and perforin); and limit viral replication through production of IFN-¥ and tumor necrosis factor (TNF)-α [40]. DC may also play a role in the state of tolerance through induction of regulatory T cells (Tregs).

In adult primary HBV infection the viral DNA is undetectable for 4–7 weeks and active replication and spread through hepatocytes lead to high viral load by

8–10 weeks of infection. In most patients with self-limited infection, the HBV DNA rapidly falls before the ALT peaks by the 12–16 weeks [40]. The early virus control is through non-cytopathic mechanisms with NK cells activation, upregulation of IFN-¥, IFNα and TNF-α induce APOBEC3 deaminase, resulting in decreased cccDNA in hepatocytes [41, 42]. Clearance of acute HBV infection follows the vigorous activation of indoleamine-2,3-dioxygenase (IDO), chemokines and cytokines increased production [42]. There is evidence that HBV and HCV impedes pattern recognition-dependent signal transduction, resulting in impaired innate immune response and chronic HBV infection is associated with impaired NK cell response with defective IFN-¥ production [40].

NK cells also appear to play an active role in spontaneous clearance of HCV, and large-scale cohort studies reveal that certain combinations of HLA-C and killer-cell inhibitory receptors (KIRs) (KIR2DL3) are associated with spontaneous HCV clearance [43]. Chronic HCV infection is associated with several immune disturbances: dysfunctional dendritic cells (DCs) resulting in impaired ability to promote Th1 polarization and IFN-α production; exhaustion of $CD8^+$ T cells, impaired stimulation of CD4 T cells and increase in Tregs. Tregs suppresses the activity of NK cells, DCs, HCV- or HBV-specific T cells, resulting in reduced liver damage and impede virus elimination [40]. Overall, T cell exhaustion and viral escape are believed to be the main mechanisms involved in HCV persistence [44]. Fully functional $CD4^+$ T cells assist in $CD8^+$ T cell mediated effector function to eliminate HCV. Exhaustion of $CD8^+$ cell is a complex mechanism that is incompletely understood, but is associated with co-expression of several inhibitory receptors such as PD-1, 2B4, and CD160 and increased levels of IL-10 [44]. HCV's escape from $CD8^+$ T cell effector function occurs in acute and chronic infection and appears to play a role in viral persistence. In chronically HCV infected patients, viral escape mutations are consistently present in about 50% of all targeted $CD8^+$ T cell epitopes, resulting in impaired epitope binding at T cell receptor and antigen processing by the proteasome [45]. Furthermore, ongoing antigen stimulation from viral escape is important for $CD8^+$ T cell exhaustion.

5.4 Therapy for Chronic Hepatitis B Infection

There are two classes of drugs available for treatment of HBV, the nucleoside or nucleotide analogs which are inhibitors of HBV polymerase, essential in viral replication, and IFN-α with direct antiviral and immune-modulatory effects. IFN-α is presently used as the long-acting pegylated form (PEG-IFNα) for ease of administration and better tolerance. IFN-α is normally stimulated as part of the innate immune response against viral infections, induce IFN-stimulated genes which act on multiple steps of the HBV replication cycle and indirectly inhibit the virus by affecting cell-mediated immunity. It was recently shown that IFN-α (and lymphotoxin-β) can induce the degradation of HBV cccDNA in infectious cell culture systems [41].

Treatment with PEG-IFN-α (subcutaneous injection) alone for 48–50 weeks in HBeAg-positive patients resulted in e-antigen seroconversion in 29–32% and surface-antigen loss of 3–7% 24 weeks after completion of therapy [46, 47]. Combination with lamivudine did not improve the outcome. The side effects of IFN-α are flu-like illness, fatigue, depression, bone marrow suppression, and exacerbation or unmasking of autoimmune diseases. HBeAg seroconversion is durable in 80% of patients and greater in genotype A (58%) than other genotypes (11%) [48]. In HBeAg-negative subjects treatment with PEG-IFN-α for a year resulted in sustained improvement in ALT and HBV DNA (<10,000 IU/ml) in 25% and HBsAg loss in 9%, 3 years after completion with no benefit of adding lamivudine [49]. In patients with HDV coinfection the only effective therapy is Peg-IFN [13].

In HBeAg-positive patients with high ALT, low HBV DNA levels and viral genotype A are predictors of response to IFN-α [50] and fall in HBsAg concentration on treatment is also s strong predictor [51]. In patients with HBeAg-negative chronic infection a decrease in HBsAg concentration after 12–24 weeks is predictive of sustained response and some studies reported that interferon lamda3/IL 28B polymorphisms may predict response [52].

The nucleos(t)ide analogs (NA) inhibit reverse transcription of the pregenomic RNA into HBV DNA and have no specific effect on the HBV cccDNA, accounting for the common viral relapse after cessation of treatment. There are five oral agents available: lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate (viread), and telbivudine, and recently tenofovir alafenamide (vemlidy) was licensed in 2016. This new formulation of tenofovir can replace viread as it has less nephrotoxic and bone toxicity potential and, thus, is safer.

Antiviral treatment for HBV main objective is to prevent progression to cirrhosis, HCC, and liver failure or liver-related mortality and eradication is not usually feasible. The main driver of disease progression is hepatic necroinflammation from the host immune response, seen during the immune clearance and reactivation phases. Table 5.1 summarizes the indications for treatment of chronic HBV infection. Should patients with CHB, no cirrhosis, normal ALT, and HBV DNA >20,000 units/ml be treated? Currently these patients are not included in the guidelines for treatment, although high HBV load is a strong predictor of liver cirrhosis and HCC. Several studies have shown that antiviral NA therapy might delay liver disease progression, reduce the risk of HCC development, and improve histological evidence of liver fibrosis or cirrhosis [53–56]. A recent nationwide, multicenter, retrospective study from South Korea has addressed this issue [57]. A total of 484 patients with CHB (HBeAg-positive), normal ALT, no cirrhosis, HBV DNA >20,000 IU/ml, mean fibrosis 4 index 1.4–1.5 were followed for a median duration of 66.5 months. After matching for propensity score, the 87 patients receiving NA soon after diagnosis had significantly decreased risk of HCC ($p = 0.004$) and cirrhosis ($p = 0.036$) than the 397 untreated controls [57]. Similar results were found in a larger and longer study from the USA and Taiwan, 591 treated with NA and 591 untreated (propensity score matched) followed for 8 years [58]. Although the results of these studies should be confirmed by a randomized, controlled trial, an argument

Table 5.1 Indications for treatment of chronic HBV infection

Patients	Treatment indication guidelines		
Groups	AASLD	APASL	EASL
$HBeAg^+$	DNA ≥20,000 IU/ml	≥20,000 IU/ml	≥2000 IU/ml
	ALT ≥2 X ULN	ALT ≥2 X ULN	>ULN
Histology	Inflam. or fibrosis	Inflam. or fibrosis	Inflam. or fibrosis
$HBeAg^-$	DNA ≥20,000 IU/ml	≥2,000 IU/ml	≥>2000 IU/ml
Histology	Inflam. or fibrosis	Inflam. or fibrosis	Inflam. or fibrosis
Cirrhosis	DNA ≥ 2000 IU/ml	≥2000 IU/ml	Detectable
Decompensation	Treat	Treat	Treat
Immunosuppressed[a]	$HBeAg^+$	HBeAg+	$HBeAg^+$
Biologics and severe immunosuppression (myeloablation/HSC, liver transplant)	$HBsAg^-$/ anti-core+	$HBsAg^-$/ anti-core+	$HBsag^-$/ anti-core+
Pregnant women	High HBV DNA	High HBV DNA	High HBV DNA

Trepo et al. [3] and Wong et al. [12]
AASLD American Association for the Study of Liver Disease; *APASL* Asian Pacific Association for the Study of the Liver; *EASL* European Association for the Study of the Liver; *ALT* alanine aminotransferase; *HBeAg* hepatitis B e antigen; *inflam* inflammation (moderate to severe); *HSC* hematopoietic stem cell
[a]Includes HIV infection

could be made to offer patients NA treatment with similar criteria as used in this report. The American guidelines suggested that treatment could be instituted for adults >40 years of age in the immune-tolerant phase with normal ALT and elevated HBV DNA >1,000,000 IU/ml with evidence of significant necroinflammation or fibrosis [13], but recent data suggest that this may be too conservative.

For young patients (<35–40 years of age) in the immune clearance phase with HBeAg-positive CHB and high ALT, it is reasonable to observe for 3–6 months before starting therapy as there is a probability of spontaneous HBeAg seroconversion and resolution of inflammation without residual liver damage, and passage into the inactive chronic carrier phase [12]. This seldom occurs in HBeAg-negative patients in the reactivation phase and antiviral treatment should be started when the HBV DNA and ALT are high. Currently, enticavir and tenofovir are the NA of choice because of low rates of resistance, 1.2% and 0% after 5 years treatment [3] and combinations of agents are not more effective than single agents. Although these two agents are considered equivalent for HBV treatment, a recent study reported that relapse was more common after stopping tenofovir than entecavir and predicted by rising HBV DNA levels in the month following discontinuation [59]. Combination of two agents may be used for lifelong therapy in HIV-coinfection to prevent development of resistance

or when resistance has developed and further long-term treatment is needed. An area of contention is duration of NA therapy for CHB. Guidelines recommend that NA can be discontinued after HBeAg-positive patients have completed 6–12 months of consolidation therapy after HbeAg seroconversion, and when HBeAg-negative patients become HBsAg-negative which usually means indefinite treatment [3]. There is some evidence that stopping NAs in some HBeAg-negative subjects before becoming HBsAg-negative can result in long-term HBsAg clearance (20%) from heightened immune response post therapy [60].

The Asian Pacific Association for the Study of the Liver recommends consideration of treatment cessation when HBV DNA is undetectable after 2 years therapy; but a study reported 45% relapsed clinically after this criterion and another 13% had virological relapse a year after stopping treatment [61]. Lifelong therapy with NA is recommended for all patients with cirrhosis. Table 5.2 summarizes the response of CHB to treatment with Peg-IFN and NA, entecavir, and tenofovir. A recent review and meta-analysis of randomized controlled trials with 2557 patients estimated the effect of antiviral NA drugs compared with placebo for the following: virological response, 43.9% vs 3.2%, p = <0.00001; biochemical response, 58.4% vs 21.9%, p = <0.00001; histological response, 59.0% vs 27.1%, p = <0.0001; seroconversion of HBeAg (anti-HBeAg), 10.7% vs 5.6%, p = 0.0005; loss of HBeAg, 14.6% vs 9.6%, p = 0.0002; but adverse events were not greater with treatment [62]. Unfortunately no data was provided for HBsAg seroconversion or loss; however, data in children indicate that antiviral therapy was not more effective than placebo in HBsAg clearance or seroconversion [63]. In a multicenter, international, observational study of 5872 CHB patients treated with NA therapy between 1997

Table 5.2 Response to treatment in chronic HBV infection

HBV status	Peg-IFN[a] (%)	Entecavir[b] (%)	Tenofovir[b] (%)
HBeAg-positive			
HBV DNA suppression	30–42 (<2000–40,000 IU/ml) 8–14 (<80 IU/ml)	61 (<50–60 IU/ml)	76 (<60 IU/ml)
HBeAg loss	32–36	22–25	–
HBeAg seroconversion	29–36	21–22	21
ALT normalization	34–52	68–81	68
HBsAg loss	2–7 (6 mths post-Rx)	2–3 (1yr)	3 (1 yr)
	11 (3 yrs post-Rx)	4–5 (2 yrs)	8 (3 yrs)
HBeAg-negative			
HBV DNA suppression	43 (<4000 IU/ml) 19 (<80 IU/ml)	90–91	93
ALT normalization	59	78–88	76
HBsAg loss	4 (6 mths post-Rx) 6 (3 yrs post-Rx)	0–1 (1 yr)	0 (yr)

Data adopted from Terrault et al. [13]
mths months; *yrs* years; *Rx* treatment; *ALT* alanine aminotransferase
[a]Assessed 6 months after completion of 12 months of therapy
[b]Assessed after 2–3 years of continuous therapy

and 2015, only 70 (1.2%) cleared HBsAg which was sustained in those who discontinued treatment [64]. However, this could be by chance even without treatment.

Should combination of NAs and IFNα be used? A recent review of NAs monotherapy versus combined NA and IFN for HBeAg-positive CHB reported better efficacy for HBeAg loss/seroconversion and undetectable HBV DNA, but no significantly difference for HBsAg seroconversion, sustained virological response rate, or biochemical response rates between the two groups [65]. In another review of entecavir alone versus entecavir and IFNα combination, the combination was superior at 48 weeks but not at >96 weeks for HBeAg seroconversion and undetectable HBV DNA [66]. A recent controlled study of PEG-IFNα plus tenofovir for 48 weeks resulted in HBsAg loss in 9% versus PEG-IFNα alone of 4% at 72 weeks [67]. However, it is arguable whether or not the small benefit of IFNα plus tenofovir justifies the cost and burden of such therapy.

Prophylactic treatment is recommended to prevent hepatitis flare and liver failure in HBsAg-positive receiving immunosuppressive therapy; HBsAg-negative and anti-HBc positive patients (anti-HBs negative) receiving potent chemotherapy for hematological malignancies or stem cell transplantation and some biologics (rituximab) should be treated with NA [68]. For pregnant women with high HBV DNA, tenofovir administration in the second or third trimester improves the prevention of mother-to-child transmission when combined with HBV immunoglobulin and vaccine, and is now recommended [69]. Another indication for prophylactic HBV NA is coinfection with HCV being treated with DAAs, as there is increasing reports of HBV reactivation and clinical hepatitis flare [70].

Surprisingly, the NA or HBV polymerase inhibitors are not effective for treatment of HDV coinfection and patients are usually treated with prolonged course of peg-IFNα plus NA for 1 year with sustained virological response of 25–30%. However, in a retrospective study from Turkey (where HDV is fairly common among people with chronic HBV) the sustained viral response increased with the duration of IFN (or multiple courses) and HBVs Ag clearance was found in 37% with very prolonged course (>2 years of IFN) [71].

5.5 Therapy for Chronic Hepatitis C Infection

The revolution in chronic HCV infection started around 2003–2004 with the marketing of PEG-IFNα and ribavirin (RBV) for treatment. Treatment for 24–48 weeks was shown to produce sustained virological response (SVR) with negative HCV RNA PCR 6 months after cessation of therapy, considered clearance or cure of the infection. This was associated with improved quality of live, improved survival, improvement of advanced liver disease (resolution of cirrhosis and portal hypertension in about 50%), and decreased risk of HCC [72–74]. However, this combination was tedious, requiring weekly subcutaneous injections, associated with many side effects (anemia, cytopenias, depression with suicidal ideation, fatigue, and flu-like symptoms), and response (40–80%) was variable and dependent on the HCV-genotype.

Although new protease inhibitors were subsequently introduced for combination with PEG-IFNα with or without RBV, the use of these agents have been replaced by the well-tolerated, oral 2–3 combination DAAs with 90–95% "cure rate" after 8–12 weeks' treatment. The dramatic effect of these novel agents can be fully appraised after reviewing data on spontaneous clearance of chronic HCV-infection. In a population based study of 10,318 HCV-infected patients (from 1994 to 2013), only 50 had documented late spontaneous clearance for an incidence of 0.36 per 100 person-years of follow-up [75]. However, spontaneous clearance of 26.9% was recently reported in a cohort of 52 pregnant women attributed to IL28B-CC genotype and late postpartum period [76].

Simeprevir and sofosbuvir were the first anti-HCV direct-acting antiviral agents (DAAs) approved by the US FDA in 2013. Currently there are 14 DAAs (see Table 5.3) for chronic HCV treatment, targeting protein processing (NS3/4A protease) and viral replication (NS5A protease and NS5B polymerase) [77–80]. Some of the agents have relative genotype-specific activity (genotypes 1–6) while others are highly pan-genotype active. Combinations of two or three agents are always used to prevent development of resistance and increase activity and efficacy. Resistant mutations may occur as natural polymorphisms or selected by prior drug treatment failures, especially with poor treatment compliance in the homeless, persons with psychiatric illness, injection drug abuse, or alcoholism. Specific HCV genotypes are more difficult to clear with DAA than others, such as genotypes 1a and 3, particularly in the presence of liver cirrhosis [80–82]. Ribavirin (RBV) can be used in combination with DAAs to allow shorter duration of therapy, selected circumstances such as cirrhosis, type 1a, prior nonresponse or failure, and presence of resistant variants to N5SA, depending on the regimen [29].

To facilitate ease of administration, decrease pill burden, and improve treatment compliance pharmaceuticals have co-formulated 2–3 drug combination in fixed-dose single pill combinations, see Table 5.4. Initially four fixed-dose combinations were marketed, named as Harvoni by Gilead (sofosbuvir/ledipasvir), Viekirax by AbbVie (parataprevir/ritonavir-ombitasvir), Zepatier by Merck (elbasvir/grazoprevir), and Epclusa by Gilead (sofosbuvir/velpatasvir) [83]; and recently two others were approved

Table 5.3 Direct antiviral agents and HCV targets

Inhibitor class	Group suffix	Agents
Targeting HCV protein processing		
NS3/4A protease	-PREVIR	Asunaprevir, glecaprevir, grazoprevir, paraitaprevir, simeprevir[a], voxilaprevir
Targeting HCV replication		
NS5B polymerase	-BUVIR	Nucleotide: sofosbuvir Nonnucleoside: dasabuvir
NS5A polymerase	-ASVIR	Daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir

Adopted from: clinicaloptions.com slide

[a]Simprevir was recently withdrawn from the market, press release by Jannsen March 2018

Table 5.4 Fixed-dose combinations of direct antiviral agents for HCV

Approved combinations			
Brand name	Pharma company	Agent/dose	Target
Epclusa	Gilead	Sofosbuvir 400 mg/velpatasvir 100 mg	NS5A-Polymerase
Harvoni	Gilead	Ledipasvir 90 mg/sofosbuvir 400 mg	NS5A-Polymerase
Holkira	Abbvie	Ombitasvir 12.5 mg/paritaprevir 75 mg/ ritonavir 50 mg	NS5A-Polymerase + NS3/4A protease
Hoikira Pak		+Dasabuvir 250 mg	NS5B polymerase
Mavyet	Abbvie	Glecaprevir 100 mg/pibrentasvir 40 mg	NS3/4A protease +NS5A polymerase
Vosevi	Gilead	Sofosbuvir 400 mg/velpatsvir 100 mg/ voxilaprevir 100 mg	NS5B/NS5A polymerase NS3/4A polymerase
Zepatier	Merck	Elbasvir 50 mg/grazoprevir 100 mg	NS5A-polymerase + NS3/4A protease

Data obtained from Soriano et al. [78]. Merck has discontinued the development of the triple combination of grazoprevir/ruzasvir/uprifosbuvir—press release September 29, 2017

by FDA, by AbbVie named Mavyet (glecaprenavir/prentasvir), and Gilead called Vosevi (sofosbuvir/velpatasvir/voxilaprevir), and one in clinical development. The latter three fixed-dose combinations will fill a niche for salvage therapy for retreatment of patients with unfavorable genotypes, resistant substitutions, and exposure to other DAAs.

The aims of treatment with DAAs are to achieve long-term suppression or SVR of the virus (virological cure), now defined as undetectable HCV-RNA 3 months post treatment (equivalent to 6 months or years later); prevention of progressive liver fibrosis, cirrhosis, hepatic failure, and HCC. Ideally all patients with HCV should be treated as soon as diagnosed but because of the huge cost for a course of therapy ($80,000–$120,000 US), guidelines have recommended treatment for patient with significant liver fibrosis (METAVIR score F2 to F4, moderate to severe fibrosis), cirrhosis (compensated or decompensated), HIV coinfection, significant extrahepatic manifestations, post-liver transplantation with HCV and others. Many developed countries now offer treatment with DAA to all patients with chronic HCV infection, except those with IVDA should abstain from drug abuse for at least >6 weeks [84]. There are no absolute contraindications to treatment except limited life expectancy when DAAs would have no significant benefit. Specific agents, however, have selective contraindications, such as sofosbuvir should not be used in patients receiving amiodarone which cannot be replaced with another cardiac drug. It is should also be avoided in the presence of severe renal impairment (estimated glomerular filtration rate <30 ml/min), as there is a higher frequency of anemia,

worsening renal function, and more severe adverse events, but response to treatment still remains high [85]. Combinations containing NS3-4A protease inhibitors, such as simprevir, ritonavir-boosted paritaprevir or grazoprevir, should not be used in patients with Child-Pugh B or C decompensated cirrhosis, or previous decompensation due to very high protease inhibitor concentrations achieved in these patients [86].

5.5.1 Choosing the Appropriate DAA Combination

With the advent of so many DAAs available it has become a daunting task to select the most appropriate and effective regimen. The selection process should be guided by data from randomized trials and the patients' profile: naïve or prior therapy, HCV-genotype, severity of liver disease (cirrhosis, compensated, or decompensated), comorbid conditions (HIV, renal impairment, etc.), present medications, and possibility of drug interactions and viable substitutions. In most cases a single fixed-drug combination is preferable but the choice may also depend on the type of drug-cost coverage (medical insurance, government programs, etc.). In most instances baseline resistant antiviral substitutions (RAS) of the HCV will not be available to guide therapy. Table 5.5 summarizes the treatment regimens for each HCV genotype.

Genotype 1 is the most prevalent subtype of HCV worldwide and among industrialized countries and data on therapeutic response to DAAs is most robust with this genotype. There are five options for treatment of this genotype and the fixed-dose combination of sofosbuvir (400 mg)/ledipasvir (90 mg) (Harvoni) is the preferred option [84]. Treatment-naïve patients with or without compensated cirrhosis can be treated with Harvoni for 12 or 8 weeks with >95% SVR, but in treatment experienced (DAAs naïve) patients adding RBV (1000 mg <75 kg, 1200 mg

Table 5.5 Preferred DAAS for HCV based on genotypes

Genotype	Naïve	Experienced	No cirrhosis/RNA (weeks)	Compensated cirrhosis (<6 million IU/ml) (weeks)
Type 1	Harvoni		8	12
		Mavyet	8	12
Type 2	Mavyet	Mavyet	8	12
	Epclusa	Epclusa	12	12
Type 3	Mavyet		8	12
	Epclusa	Epclusa	12	12
Type 4	Mavyet	Mavyet	8	12
	Harvoni		12	12
	Epclusa		12	12
Types 5 and 6	Mavyet	Mavyet	8	12
	Harvoni	Harvoni	12	12
	Vosevi	Vosevi	12	12

>75 kg) improves the SVR from 86% to 97% [85]. However, in patients with decompensated cirrhosis Harvoni plus RBV for 12 weeks result in SVR in 85–87% of cases. Treatment can be shortened to 8 weeks with the fixed-dose combination alone in treatment-naïve patients without cirrhosis and HCV RNA <6 million IU/ml [85]. For IFN/RBV experienced patients with genotype 1 with no cirrhosis, a simpler and shorter regimen is the fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) (Mavyet) for 8 weeks, but 12 weeks for patients with cirrhosis [87].

In genotype 2 patients the European (EASL) guidelines [84] list two first-line treatment options, fixed-dose combination sofosbuvir/velpastasvir (Epclusa) or the combination of sofosbuvir (400 mg) and daclatasvir (60 mg) for 12 weeks for treatment naïve or IFN/RBV experienced patients with SVR >95%. In patients with compensated cirrhosis Epclusa for 12 weeks appears to be superior to sofosbuvir/daclatasvir which should be given for at least 16 weeks. However, the fixed-dose Mavyet (glecaprevir/pibrentasvir) may be considered as a better first option, as treatment in naïve or experienced (IFN/RBV or Sofosbuvir/RBV±IFN) patients with genotype 2 without cirrhosis treated for 8 weeks resulted in 98% SVR, but 12 weeks for those with compensated cirrhosis [88].

For genotype 3 infected patients without cirrhosis, naïve or IFN/RBV experienced, both EASL and the American guidelines (AASLDS/IDSA) recommend Epclusa for 12 weeks, and for naïve patients Mavyret for 8 weeks is considered a first option by AASLD/IDSA [84, 86]. In patients with compensated cirrhosis naïve to treatment Epclusa or Mavyret for 12 weeks are considered first options, but in IFN/RBV experienced patients the fixed-dose triple combination Vosevi (sofosbuvir/velatasvir/voxilaprevir) or the dual combination Zepatier plus sofosbuvir for 12 weeks [89].

Genotype 4 infected treatment-naive patients with or without compensated cirrhosis first options include Harvoni, Epclusa and Mavyret for 12 weeks, but the latter can be given for 8 weeks in treatment-naïve or IFN/RBV experienced subjects without cirrhosis [87]. In treatment-experienced patients with or without compensated cirrhosis Harvoni should be combined with weight-based RBV for 12 weeks [29]. Eight weeks of Mavyret (glecaprevir/pibrentasvir) is the preferred choice for those without cirrhosis but all regimens should be given for 12 weeks in those with compensated cirrhosis [87].

Experience and data from therapeutic trials are the lowest for HCV genotypes 5 and 6. Three fixed-dose combination agents are the best options: Harvoni, Vosevi and Mavryet for naïve or IFN/RBV experienced patients for 12 weeks with or without compensated cirrhosis, except the latter for 8 weeks in subjects without cirrhosis [86]. Three fixed combinations have pan-genotypic coverage, Epclusa, Mavyret and Vosevi, but the course of Mavyret is the least expensive as a recent study shows that this combination can be used for all naïve patients ($n = 280$), except genotype 3, for 8 weeks with or without compensated cirrhosis [88].

5.5.2 *Management of Special Populations with HCV Infection*

In patients with decompensated cirrhosis not waiting for liver transplantation treatment with DAAs can improve liver function and survival. Several trials have demonstrated high SVR, similar for Child-Pugh B and C patients, and improvement in liver function and short-term survival [88]. Adverse-free events at 15 months associated with SVR is greater for those with Child-Pugh B than -C cirrhosis [89, 90]. Long-term follow-up data are lacking but pending. Protease inhibitors are not recommended for patients with Child-Pugh B or C decompensated cirrhosis. Guidelines recommend two fixed-dose combinations (Harvoni and Epclusa) plus RBV for 12 weeks for patients with genotypes 1, 4, 5, or 6 [83, 84], and for those with genotypes 2 or 3 can be treated with Epclusa plus RBV or sofosbuvir, daclatasvir and RBV for 12 weeks [84]. The latter combination can also be used in genotypes in genotypes 1, 4, 5, or 6.

HCV coinfection is estimated to occur in 10–30% of all HIV-infected individuals and up to 90% of HIV-infected IVDAs, with a global prevalence of 2.5–5 million people [91]. HIV results in more rapid progression of liver fibrosis and liver complications (including hepatic decompensation) than HCV alone and early treatment with DAAs is a priority. However, highly active antiretroviral agents (ART) should be started first with evidence of HIV suppression with undetectable virus or HIV RNA <50 copies/ml. All DAAs in HIV/HCV-coinfected patients with compensated cirrhosis are safe and effective with SVR >90% [92]. The major concern is drug interaction of ART with DAAs and adjustment in ART may be needed until treatment for HCV is completed. The input of a HIV-experienced pharmacist is indispensable. The drug interactions and pharmacologic considerations in HIV/HCV-coinfected persons were recently reviewed and will not be dealt further [93].

Chronic kidney disease (CKD) is associated with HCV infection with an increased risk of end stage renal disease (ESRD) and increased mortality in those on dialysis [94, 95]. Sofosbuvir combinations are not recommended by the European guidelines [84] for severe renal dysfunction (eGFR <30 ml/min), as the drug is eliminated mainly by the kidneys and safety is a concern with further deterioration in function. Also in patients with ESRD on dialysis the appropriate dose is not established. However, the American guidelines include sofosbuvir combinations for patients with severe renal dysfunction with careful monitoring [86], based on recent reports of safety in patients with ESRD on dialysis [96, 97]. Sofosbuvir-free regimens that have been found to be safe and effective in severe CKD, recommended by guidelines, include fixed-dose combinations Zepatier (elbsvir/grazoprevir) and Mavyret (glecaprevir/pibrentasvir) [98, 99]. In industrialized countries 10% of renal transplant patients have chronic HCV and are suitable for DAAs treatment, but limited data exist on their efficacy and tolerance in this group. In a recent randomized, phase 2 study Harvoni for 12 or 24 weeks was shown to be highly effective and well tolerated in kidney transplant recipients and HCV genotype 1 and 4 [100].

Persons who inject drugs represent the highest proportion of people in high-income countries with chronic HCV infection, with estimated prevalence of

60–80% [101, 102]. However, most clinical trials of DAAs exclude patients with recent drug abuse. In a pharmaceutical-funded randomized, controlled, international trial 301 treatment-naïve IVDAs with chronic HCV genotypes 1, 4 or 6 infection, who were at least 80% adherent to visits for opioid agonist therapy, were randomized to immediate or delayed treatment with Zepatier for 12 weeks [103]. Ongoing drug abuse was not an exclusion criterion. The SVR was 91.5% in the immediate therapy group and 89.5% in the delayed-treatment group. Among 18 patients with post-treatment viral relapse only 6 had reinfection, but continued drug abuse did not affect adherence or efficacy. It is unclear form this trial, however, whether or not similar success can be obtained in IVDAs not on opioid agonist supervised therapy. In a cohort of 257 patients with HIV/HCV coinfection and SVR after DAAS, reinfection rate the first year after SVR was highest in those with high frequency injection drug use (injection of cocaine or methamphetamines, which are associated with multiple injections per day) and high-risk sexual behavior among MSM [104]. While the majority of patients with reinfection had different HCV genotype, some patients with recurrence occurred more than 2.5 years later had the same genotype, suggestive of reinfection rather than late relapse. Phylogenetic analysis of late recurrent viremia can distinguish virological relapse from reinfection. In a study of patients with SVR after 12 weeks post-DAA therapy, at 24 weeks follow-up only 12 of 3004 patients had later recurrent HCV viremia [105]. Phylogenetic analysis demonstrated that 58% (7 of 12) were reinfection and only 5 (0.17%) of the entire cohort had true late relapse. However, it would be useful to extend this study for another 2–3 years.

Patients who failed DAAS have limited retreatment options. The absolute number of such patients is accumulating and is now substantial with increasing use of DAAs. The majority of these patients had previously received a NS5A inhibitor (i.e., ledipasvir or daclatasvir) containing regimen [105]. Resistant mutations or substitutions selected by the NS5A inhibitors maintain viral fitness long after the end of the failed regimen [106]. The triple combination of sofosbuvir (nucleotide polymerase inhibitor), velpatasvir (NS5A inhibitor), and voxilaprevir (protease inhibitor), fixed-dose combination (Vosevi) for 12 weeks, has been shown to be highly effective with SVR 96–98% in patients with HCV genotypes 1, 2, 3, or 4 previously treated with DAAs with or without a NS5A containing regimens, with or without compensated cirrhosis [107]. The data was combined from two phase 3 trials (POLARIS-1 and POLARIS-4) and resistant viral substitutions to NS3 or NS5A inhibitors at baseline were present in 83% and 49% of the patients HCV in the two studies. Thus, despite the high frequency of resistant substitutions to NS3 and NS5A inhibitors the triple combination was highly effective. An alternative regimen for failed treatment with DAAs containing an NS5A inhibitor, genotype 1 with or without compensated cirrhosis, is the fixed-dose combination Mavyret (glycaprevir/pibrentasvir) for 16 weeks, with SVR of 94% [108, 109]. These fixed combinations are preferable to more complex regimens for retreatment, which also achieved >95% SVR, such as sofosbuvir/grazoprevir/elbasvir plus ribavirin for 16 weeks [110].

5.5.3 Controversy Regarding Efficacy of Antiviral Therapy of HCV

Most guidelines and reviews recommend DAAs as highly effective drugs for chronic HCV with long-term SVR or putative cure of >90%. However, a recent Cochrane Review concluded that there was insufficient evidence to confirm or reject the benefit of DAA therapy on HCV-related complications or mortality as the duration of the trials were not long enough [111]. The authors of the review also concluded that the clinical relevance of SVR used in the DAAs trials is questionable and that it is not validated surrogate test of clinical outcome. Technically the initial criticism is correct that of the 84 trials involving DAAs none proved clinical efficacy with long-term follow-up to show significant decreased risk of cirrhosis or HCC. The IDSA/AASLD has responded to the Cochrane Review concerns with satisfactory and gratifying response [112], which is summarized. A key issue in the argument by the reviewers is the validity of SVR as a proven surrogate marker of clinical outcome in chronic HCV infection. The US FDA accepted SVR as a valid surrogate marker for outcome based on accumulative data from earlier IFN-containing treatment. Late relapse after attaining SVR is rare and that achievement of SVR is associated with decreased HCV-related morbidity and mortality. In patients with HCV-associated advanced liver fibrosis, SVR is correlated with >70% decreased risk of HCC and 90% reduction of liver-related mortality and liver transplantation [69–71]. Also, a review and meta-analysis of the survival benefit of achieving SVR in HCV-infected patients in 2015 confirmed a significant survival benefit compared to unsuccessful treatment, from data of 31 studies with 33,360 patients [113]. Furthermore, a recent large case control study of 6970 DAA-treated cases and 6970 propensity-score, matched untreated controls with chronic HCV showed a 57% reduction in mortality within 18 months of DAA-therapy [114]. More recently, in 2200 patients with HCV-related cirrhosis the incidence of HCC was analyzed from prospectively collected data in patients treated with DAAs with or without SVR [115]. At 1 year, the cumulative incidence of HCC was significantly lower in those with SVR versus those who failed, 2% vs 7%, respectively, in Child-Pugh class A cirrhosis and 8% vs 12% for those with Child-Pugh class B cirrhosis. Hence current recommendations and guidelines for treating chronic HCV with DAAs are valid and there is no need to wait on longer term clinical trials.

An indirect benefit of DAA is the ability to use organs from HCV-infected subjects for organ transplantation to uninfected recipients by initiating antiviral agents within a few hours after transplantation for 4 weeks, which have been shown to prevent establishment of HCV infection [116].

5.5.4 Concerns of Cost of Treating HCV

DAAs' high cost has limited the access of these medications to the poor in the USA without drug insurance and Medicaid is rationing these drugs for those with more severe liver fibrosis. Different policies exist in high income countries for access of

novel but expensive, essential medicines. Canada (with socialized medicine) initially restricted DAAs to those with more advanced liver fibrosis and all HIV coinfected persons, but as of February 2018 the Ontario Provincial Drug Benefit Program allows DAAs for all HCV-RNA positive patients irrespective of fibrosis score. Based on their efficacy and safety profile all patients should be treated with chronic HCV infection. It is estimated that at current cost to treat 3 million people in the USA would cost >250 billion dollars [117]. A 12-week course of Harvoni cost $94,500 and Viekira Pak cost $83,319 (US) for the same duration. Despite the high cost of DAAs these agents are considered cost effective [118].

There is a large variation in price of DAAs internationally, a 12-week course of sofosbuvir in the USA costs $84,000 but in Egypt only $900 [117]. India denied Gilead a patent for sofosbuvir and allowed generic manufactures to sell 12 weeks of sofosbuvir for <$250 [117]. Recently Medicins Sans Frontiers struck a deal with generic manufacturers to buy DAAs for as little as $1.40 a day (Hirsher B, Neely J. MSF charity secure generic hepatitis C drugs for $1.40 a day. Reuters, October 31, 2017). Patent laws in industrialized countries protect pharmaceuticals to sell new drugs at very high cost for 10–20 years before allowing sale of cheaper generic drugs. In the USA it has been proposed to set up a federal-assisted program on the model of the AIDS Drug Assistance Programs to provide free or affordable DAAs to the poor in need [117]. Another avenue that should be explored by advocacy groups includes determining the legality of ordering or assisting patients to order DAAs online from generic manufacturers in developing countries. Brazil was able to secure a 90% discount price for sofosbuvir–daclatasvir and has plans to enable local production of generic versions of these drugs at one-quarter the current price [119].

5.6 Future Treatment of Chronic Hepatitis B

There is growing interest in finding a cure for chronic HBV infection. Several experimental HBV drugs are in late preclinical or early clinical phase of development. These can be classified according to the target or mechanism of action: (1) direct-acting antivirals: (a) new polymerase inhibitors (prodrug of tenofovir), (b) capsid inhibitors, (c) assembly/HBsAg inhibitors, (d) and RNA inhibitors or antisense drugs; (2) host targeting agents, i.e., entry inhibitors, cyclophilins, glucosidase and others; (a) immune modulatory agents, i.e., Toll-like receptor-7 agonist, programmed death-1 (PD-1) blockade, RIG-1 and NOD2 activation, and therapeutic vaccines [120]. However, these agents seem unlikely to achieve cure with short-term therapy as seen with DAAS for HCV. Eradication of HBV cccDNA appears to be necessary for the cure of chronic HBV which is difficult to achieve. The HBV cccDNA is secluded in the hepatocytes nucleus and avoids clearance from the host immune response.

An indirect approach is the combination of agents targeting different steps of HBV replication that may completely inhibit HBV DNA replication and enhances the reduction of cccDNA. Another technique is to target RNaseH, which is required for HBV replication and cccDNA formation and potential inhibitors have been identified [120]. Currently there is no promising agent identified that can block HBV cccDNA formation or enhance the degradation directly. Combination of disubstituted sulfonamides to block formation of cccDNA [121] and IFNα to reduce production of virions may result in functional cure [122], but may not produce cure after stopping treatment. Understanding the precise molecular mechanism for conversion of the relaxed circular (RC) DNA to cccDNA and factors regulating its function and metabolism is the key to finding a cure for HBV.

New effective drugs are clearly needed for HDV and new basic research have led to some progress in this field. Interestingly, a relatively new anti-diabetic oral medication, rosiglitazone, has anti-HDV activity and should be studied for its efficacy in combination with NA for coinfected patients [123]. Lonafarnib, a prenylate inhibitor, boosted with ritonavir to increase the half-life, in preliminary studies appears promising in suppressing HDV RNA but would need to be combined with a NA since it has no HBV activity [124].

5.7 Issues in Prevention of HBV

Despite the availability of an effective HBV vaccine, many developing countries with high prevalence of HBV are not utilizing the vaccine at birth to prevent mother to child transmission. Only 92 of 193 countries (48%) report administering the vaccine at birth, despite WHO recommendations [125]. The vaccine is administered at birth in 10% of neonates in sub-Saharan Africa with only 11 of 47 African countries introduced HBV vaccination at birth. Hence, about 1% of newborns (>350,000) annually are infected with HBV at birth in sub-Saharan Africa [126]. However, even with universal HBV-immune globulin and 3–4 doses of vaccine after birth neonatal transmission has been reported in up to 12% of newborns, when the mother has high HBV DNA (>200,000 IU/ml) or HBeag-positive [127]. This led to studies in China which showed almost zero neonatal transmission with antiviral treatment of high-risk women and neonatal vaccination [128]. Recently, a study from Thailand showed that administration of HBV immune globulin with the first of four HBV vaccine doses given <4 h after birth (rather than 6 weeks) resulted in neonatal transmission of only 2% in women with HBV DNA >200,000 IU/ml [127]. As a result treatment of maternal HBV in the third trimester with tenofovir was not significantly lower. Future studies should compare immediate HBV immune globulin/vaccination after birth to third trimester tenofovir alone in women with chronic HBV, as the latter regimen may be more suitable for African countries to adopt.

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Chapter 6
Infectious Complications of Biological Agents

6.1 Introduction

Immunosuppressive disease-modifying antirheumatic drugs [DMARDs] have been used for many decades for rheumatic and other autoimmune disorders with moderate efficacy. These agents are sometimes used as monotherapy but are more commonly used in combination to improve response. The DMARDS include glucocorticoids [steroids], methotrexate [MXT], hydroxychloroquine [HCQ], sulfasalazine [SSZ], azathioprine [AZA], and less commonly leflunomide, cyclosporine, and cyclophosphamide [CPP]. Some of these agents have been linked with infectious complications especially steroids, CPP, MXT, AZA, and cyclosporine, while others such as SSZ, HCQ, gold, and leflunomide were not associated with increased vulnerability to infections but have an anti-inflammatory effect.

Since the late 1990s, advances in immunology, molecular biology, and drug development led to new approaches for the treatment of inflammatory autoimmune disorders with a plethora of novel biological response modifiers [BRM] marketed in the past 15 years. These BRMs have resulted in impressive responses in many of these conditions refractory to standard DMARDs, but there are increasing reports of severe infectious complications that were often undetected in phase III clinical trials. Biological agents have now been extended to the treatment of various cancers which failed standard chemotherapy and the field of organ transplantation pharmatherapeutics.

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6.2 Standard DMARDs Immune Effects and Infections

6.2.1 Corticosteroids

Systemic steroids are probably the most commonly used agents for rheumatic and autoimmune disorders. Corticosteroids have a broad range of inhibitory effects on the immune responses, affecting multiple types of immune cells, and are efficacious for a wide variety of inflammatory disorders. Steroids diffuse across the cell membrane to bind to the intracellular glucocorticoid receptor forming a complex that translocates in the nucleus, interacting with DNA sequences and other transcription factors [1]. The anti-inflammatory effects result from blocking the promoter sites of proinflammatory genes for interleukin-1 [IL-1] α and IL-β. Moreover, steroids inhibit secretion of inflammatory cytokines by affecting posttranslational events and downregulate gene expression of IL-1, IL-2, IL-6, IL-8, tumor necrosis factor [TNF], and granulocyte-macrophage colony stimulating factor [G-M CSF] [1].

Acute administration of systemic steroids results in neutrophilic leukocytosis, dramatic reductions in eosinophils, and lessor reductions in lymphocytes. Corticosteroids have marked effects on the cellular function of leucocytes and endothelial cells, reducing adherence of leukocytes to vascular endothelium and impairing transmigration from the circulation into infected or injured tissues to suppress the inflammatory response.

The phagocytic function and bactericidal activities of neutrophils are not affected by low-to-moderate doses of steroids although high doses may impair phagocytosis. Doses of less than 40 mg/day in adults or <1 mg/kg/day in children are considered low-to-moderate [1]. Steroids also inhibit transmigration of monocytes/ macrophages into tissues, diminish their inflammatory cytokines [IL-1, TNF], inhibit macrophage phagocytic and microbicidal functions and reduce clearance of opsonized bacteria by the reticuloendothelial system [1, 2]. They also markedly reduce circulating dendritic cells and impair their antigen-presenting function in stimulating naive T cells, reducing the development of immunity to newly encountered antigens.

Steroids have minimal effect on B-lymphocytes numbers and function but high doses can produce a short-term reduction of IgG and IgA by 10–20%. Low-moderate doses of steroids cause a slight reduction of circulating T lymphocytes with greater effect on the immature, naïve CD4+ T cells than more mature CD4+ effector cells and other subsets. High doses of steroids produce rapid depletion of most circulating T cells by enhanced circulatory emigration, inhibition of T cell growth factor [IL-2] and signaling, impaired release from lymphoid tissues, and induction of apoptosis [1, 3]. Treatment with steroids can cause a shift in the expression Th2-derived cytokines relative to Th1 cytokines by activated T-helper cells, as the inhibitory effect is greater on the expression of Th-1 cytokines. However, reports on steroid effect on delayed hypersensitivity reactions have been variable. Steroids also have inhibitory effects on eosinophils number and function and inhibit mast cell production of cytokines and degranulation.

Systemic steroids result in increased risk for a variety of infections which is related to the dose and intensity, duration of treatment, and patient-specific factors. Older age and underlying disease can influence the risk and type of infections. A previous meta-analysis of 71 controlled trials comparing the infectious complications of steroids versus placebo, reported that infections occurred in 12.7% of treated patients versus 8.0% in controls, relative risk [RR] 1.6, $p < 0.001$ [4]. The rate of infection was not increased in patients given <10 mg/day or a cumulative dose of <700 mg of prednisone, and infectious complications were greatest in patients with neurological diseases [RR = 2.8]. However, the number of patients with rheumatic disorders was relatively small. In a large nested case-control study of older patients with rheumatoid arthritis [RA], current and very recent doses had the highest impact on infectious risk with current use of 30 mg prednisone for the past 6 months, for the past 3 months, and past 28 days showing adjusted odds ratio [OR] of 9.81, 4.82, and 1.84, respectively [5]. However, even smaller doses taken up to 2.5 years were also associated with increased but lower risk of infection. The increased risk of infection associated with 5 mg of prednisone taken for the last 3 years was similar to that associated with 30 mg taken for the last month. A current user of 5 mg prednisone continuously had increased risk of serious infection compared to nonusers of 30%, 46%, 100% for the last 3 months, 6 months, or 3 years [5]. Similarly, in patients with systemic lupus erythematosus [SLE], not on other immunosuppressive agents, the infectious risk rose from 1.5-fold on prednisone dose <10 mg/day to over eightfold in patients with more severe disease receiving 40 mg/day [6].

Longitudinal observational study of 16,788 RA patients over 3.5 years in the USA previously found that prednisone use increased the risk of pneumonia hospitalization in a dose-related relationship [7]. The hazard ratio [HR] increased from 1.4 with ≤5 mg to 2.3 with >10 mg/day. Even short-term use of steroids for nonrheumatic conditions has been associated with an increased incidence of severe infections. In a large population-based cohort study of 327,452 patients prescribed short-term steroids over a 3 year period, within 30 days of drug initiation [median dose 20 mg prednisone/day] there was increased in rate of sepsis [incidence rate ratio 5.30, 95% CI 3.80–7.4], but the absolute risk for hospital admission for sepsis was low, 0.05% [8]. The increased risk persisted even with a dose <20 mg/day [incidence rate ratio 4.02].

Common viral [mainly herpes group viruses], bacterial [*Staphylococcus aureus* and others] and fungal [primarily Candida species] pathogens are the most common causes of serious infections in patients on steroids [9]. Opportunistic infections including intracellular organisms mainly occur as complications of moderate to high doses of prednisone [>15 mg/day] for prolonged periods >3–4 weeks. Herpes zoster, however, may occur more commonly in patients even on low-dose steroids. Data from >28,000 RA patients indicated that prednisone ≥7.5 mg was an independent risk factor for herpes zoster reactivation [10]. Other intracellular pathogens reactivation seen with moderate to high doses of steroids for an extended period of time, include *Mycobacterium tuberculosis* [MTB], *Pneumocystis jirovecii* [PJ], cytomegalovirus [CMV], *Listeria monocytogenes*, and parasites such as *Toxoplasma*

gondii and *Strongyloides stercoralis*. In a nationwide observational, prospective study of newly diagnosed autoimmune disease patients treated with moderate doses of steroids, the incidence of serious infections was monitored in 604 Japanese patients over 2 years [11]. There were 127 serious infections [21% of patients] and of these 43 serious intracellular infections [33.8% of infections] occurred resulting in 8 deaths. The risk factors associated with increased intracellular infections included diabetes, lymphocytopenia [≤1000/μL] and use of high-dose steroids [>30 mg/day]. Most intracellular infections occurred within 4 months and included CMV [n = 14], herpes zoster [n = 7], PJ pneumonia [PJP] [n = 7], MTB [n = 2], Epstein-Barr virus [n = 1], *Listeria monocytogenes* [N = 1] and non-tuberculosis mycobacteria [n = 1].

6.2.2 Methotrexate

MXT is a mainline therapy for patients with RA and is effective as monotherapy for many patients but is more commonly used in combination with other DMARDs. It is also used for other chronic inflammatory conditions and graft-versus-host diseases. It is a folate antagonist with anti-inflammatory and modest immunosuppressive properties. MXT can cause lymphopenia by apoptosis and clonal deletion of activated peripheral T cells and decrease lymphocyte function [12, 13]. At the doses used in RA, MXT is immunomodulatory but not significantly immunosuppressive unless used with steroids, other DMARDs or biologics. However, the weekly doses used for rheumatic disorders can affect T cell activity and several isolated cases of PJP have been reported with low-dose MXT [14, 15]. Other opportunistic infections occasionally reported with low-dose MXT include CMV pneumonia, cryptococcosis, herpes zoster, nocardiosis, histoplasmosis, aspergillosis, tuberculosis, listeria meningitis, and herpes simplex hepatitis [16–18]. The risk of infection in an RA cohort followed for 7729 patient-years taking MXT is small and the ORs for confirmed infections or infections requiring hospitalization were 0.96 and 0.91, respectively [19]. However, the risk of infection increases with concomitant use of steroids, comorbid illness such as diabetes, and disease severity, including the presence of prosthetic joints.

6.2.3 Azathioprine

AZA is a second-line agent for rheumatic diseases and concerns about its short-term and long-term toxic effects have limited its use. Its use in RA is limited to patients with severe, active, erosive disease unresponsive to conventional DMARDs; but it is more commonly used in patients with vasculitis and organ transplantation. AZA is immunosuppressive and mutagenic in animals and may increase patients risk of neoplasia. It is slow acting and the effects may persist after the drug is discontinued.

The drug is a purine analog that suppresses lymphocyte proliferation, reduce T cell numbers, and inhibit T cell function, including cellular cytotoxicity. Its effect is dose and duration dependent. Infection occurs overall in up to 9% of patients on this agent [20, 21]. Bacterial infections usually occur as a complication of drug-induced leucopenia [22, 23], and viral infections, especially herpes zoster, occur in up to 6% of treated patients [21, 23]. In patients with chronic viral hepatitis reactivation or exacerbations can occur but this is seen with other DMARDs as well [24].

6.2.4 Cyclosporine and Cyclophosphamide

Cyclosporine is a potent immunosuppressant that has been mainly used for prevention of rejection in organ transplant in combination with steroids and mycophenolate mofetil, but the use is being replaced in many centers by tacrolimus. It is only used occasionally in severe psoriasis and rheumatic diseases for aggressive disease unresponsive to conventional therapy. Cyclosporine selectively inhibits activation of T-helper cells [25]. Its use for rheumatic and autoimmune disorders is almost entirely replaced by biological agents. When used in combination with other immune suppressants, it is associated with a wide spectrum of infectious complications, bacterial, viral, parasitic, and opportunistic pathogens [26].

CPP is a potent antineoplastic immunosuppressant mainly indicated for neoplastic diseases. Its off-label use for autoimmune disorders included multiple sclerosis [MS], granulomatosis polyangiitis vasculitis, lupus nephritis, and rarely [before the advent of biologics] refractory juvenile RA. CPP is an alkylating agent of the nitrogen mustard group. Infectious complications primarily occur as a result of severe neutropenia, involving bacterial and fungal pathogens. Table 6.1 summarizes the immune mechanisms and risk of infection with standard DMARDs.

Table 6.1 Risk of infections with standard DMARDs

Agents	Immune impairment	Risk of infection	Types of infection
Steroids	Innate, T cell function [acute], [chronic use]	1.5- to 8-fold increase dose and duration effect	Acutely bacterial, viruses, TB, OIs, parasitic, fungal infections
MXT	Mild lymphocyte dysfunction	Modest increase	VZV, HSV, OIs with steroids
AZA	T cell function, neutropenia	9%	VZV, HBV reactivation, bacterial infections with neutropenia
CYP	Inhibits T-helper cells	Moderate increase	Viral, bacterial, parasitic OIs with other immunosuppressant
CPP	Neutropenia	High with neutropenia	Bacterial and fungal
HCQ SSZ	None	Not increased	None

AZA azathioprine, *CYP* cyclosporine, *CPP* cyclophosphamide; MXt methotrexate, *HCQ* hydroxychloroquine, *HSV* herpes simplex virus, *OI* opportunistic infections, *HBV* hepatitis B virus, *SSZ* sulfasalazine, *TB* tuberculosis, *VZV* varicella zoster virus

6.3 Cytokines and Immune System

Spontaneous activation of the immune cascade and stimulation of the network of proinflammatory cytokines, by thymus-derived T cells and bone marrow-derived B cells, are responsible for the clinical manifestations of rheumatic and autoimmune inflammatory conditions. The T helper [Th] lymphocytes secrete an array of cytokines, depending on the cell subsets, that influence and maintain systemic inflammation. Th-cells were classically divided into two main subsets, Th1 and Th2, with different effects on the immune system, but subsequently, Th17 cells and regulatory T cells [T reg] were described. The cytokines produced by Th1 and Th2 cells inhibit each other phenotype cellular function [27]. Th2 or B-lymphocytes are responsible for antibody production after differentiating into plasma cells and represent the cornerstone of the adaptive immunity to protect against bacterial and viral invaders.

B cells also activate T cells and promote the production of cytokines, including IL-1, 4, 6, 8, 10, and 12, TNFα, vascular endothelial growth factor [VEGF], and monocyte chemotactic protein [MCP] [28].

Th1 lymphocytes are the mainstay of the cellular immune response and the cytokines they generate mediate the inflammation in RA, psoriatic arthritis, psoriasis, acute rejection, graft-versus-host disease, and others [29]. Th1 proinflammatory mediators include TNF, interferon gamma [IFN-¥], and IL-2, and the latter two cytokines can inhibit Th2 cell proliferation. The products of Th1 cells activate macrophages, natural killer [NK] cells, and CD8+ T cells and are involved in the systemic immunity particularly against intracellular pathogens. Th2 lymphocytes are key components of the humoral immunity and stimulate antibody production by B cells and activate eosinophils, mast cells, basophils, and macrophages and are important for barrier defense at the mucosal and epithelial barrier [30]. Activation of Th2 cells plays a role in SLE, systemic sclerosis, and chronic graft-versus-host disease. Some of the cytokines produced by Th2 cells include IL-4, -5, -10 and -13 and IL-4 and IL-10 can inhibit Th1 cytokine production [28]. Th2 cells also mediate allergic diseases and asthma.

Th17 cells develop from naive T cells as a result of stimulation from antigen, transforming growth factor [TGF] beta, IL-6, and IL-23 [29]. Th17 lymphocytes secrete cytokines, IL-16, IL-17, and TNFα, recruit neutrophils to sites of inflammation and are important for defense against extracellular bacteria [30]. Th17 cells are implicated in some specific organ autoimmunity with arthritis and MS. T reg-cells function to regulate the immune response of other T cells and suppress autoimmune responses. T reg-cells suppress immune response by inhibition of CD4+ and CD8+ T lymphocytes through IL-10 and TGF-β. Impaired function of T reg-cells may be important in several rheumatic diseases, including RA, SLE, spondyloarthritis, Sjogren's syndrome, giant cell arteritis, and granulomatosis with polyangiitis [29]. ThF cells are localized to lymph glands and are follicle-honing helpers of B cells derived from variants of Th1, Th2, or Th17 cells. ThF cells can cause systemic autoimmunity and autoantibody production or contribute to T cell-mediated organ specific autoimmunity [30].

The immune system has evolved to differentiate between self and non-self for protection against invading microbes without harming self-tissues. A sophisticated system of regulatory mechanisms controls autoreactivity and allows tolerance of self-antigens by deletion or modification of autoreactive cells. Failure of the regulatory mechanisms of the immune cells results in autoimmune disorders, through genetic, epigenetic, and environmental factors. In rheumatic and autoimmune disorders, such as RA and SLE, defective immune regulation results in proliferation of autoreactive pathogenic T cells and B cells that produce autoreactive antibodies and cytokines resulting in inflammation and tissue damage. Both RA and SLE are primarily self-antibodies mediated but T cells also have a major role in the pathogenesis. In these conditions, there is an imbalance between proinflammatory Th17 cells [increase] and Treg-cells [decrease] with decrease IL-2 production and aberrant T cell signaling [31].

6.4 Biological Response Modifiers [BRM]

The development of monoclonal antibodies in the 1970s led to the advent of biological agents for therapeutics in rheumatic diseases. These BRM are made by molecular biological techniques and small molecule kinase inhibitors. The BRM modify the immune response by three mechanisms: (1) interfere with cytokine production or function, (2) inhibit the "second signal" needed for T cell activation, and (3) deplete B cells [29]. Thus, this result in nonspecific suppression of the immune system, rather than targeting autoreactive cells, which leads to infectious complications.

6.4.1 Anticytokines

Inhibition of the effector functions of cytokines has been achieved by three methods: (1) soluble receptor antagonists, example etanercept [A fusion protein of a TNF receptor linked to the Fc portion of human IgG1] binds to the target receptor in serum preventing the cytokine interaction with its cell surface receptors. (2) Monoclonal antibodies [mAbs] to cytokines or their receptors that bind to their target in serum or when bound to cell surface, and have greater affinity than soluble receptor antagonists. (3) Receptor cell surface antagonists which are biologically inactive proteins but bind to the membrane receptor of the cytokine [29]. An indirect approach is the use of small molecule drugs for oral use, that inhibits selected cytoplasmic protein tyrosine kinases, i.e., Janus kinase [JAK], to interrupt signaling from membrane cytokine receptors [29].

6.4.2 TNF Biologic Inhibitors

TNFα plays a central role in the pathophysiology of the immune response to infection and development of inflammation. It promotes the expression of adhesion molecules, enhancing the influx of immune cells at the sites of inflammation, induces the release of proteolytic enzymes, and stimulates production and upregulation of other proinflammatory cytokines [32]. Thus, TNFα is important in the pathogenesis of RA and autoinflammatory conditions and is essential for granulomatous reactions and the host response to tuberculosis.

The first BRMs for treatment of RA [introduced in the 1990s] were mAbs specific for TNF [suffix -mab], infliximab, and adalimumab. Currently there are five TNF inhibitors for the treatment of rheumatic and other autoimmune diseases. Two other mAbs, certolizumab and golimumab, and the soluble receptor antagonist etanercept, a fusion protein of p75 TNF receptor linked to the Fc portion of human IgG1 [29]. Review of the literature indicates that all five agents are equally effective and superior to MXT alone, are relatively safe in comparison and combination with MXT is superior to single agent [33]. These agents are used for RA, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease [IBD], Crohn's disease and ulcerative colitis [UC], but etanercept is not effective for UC. Infliximab is the only one requiring intravenous [IV] infusion about every 6 weeks but the others are given by subcutaneous injection every 2–4 weeks.

6.4.3 IL-1 Inhibitors

IL-1 is another proinflammatory cytokine induced in infection and cell disturbance, trauma, crystals, complement activation, and presence of immune complexes that leads to increased adhesion molecules, T cell activation, and protease production. It is important in systemic inflammation and joint damage in animal models of arthritis [34].

IL-1 inhibitors are used in patients with RA and other autoinflammatory conditions. However, they have modest effect in RA compared to TNF inhibitors and less commonly used in this condition [29]. They are not recommended for combination with other BRMs because of increased adverse events and serious infections, but can be used with MXT for RA with improved efficacy. IL-1 inhibitors have inhibitory effect on the inflammasome which is a primary mediator in autoinflammatory conditions. They are effective for the rare autoinflammatory disorders such as cryopyrin-associated periodic syndromes [CAPS], TNF receptor-1 associated periodic syndrome [TRAPS], systemic juvenile idiopathic arthritis, and adult Still's disease [29]. The three IL-1 inhibitors available include anakinra, canakinumab, and rilonacept.

Anakinra is a recombinant human IL-1 receptor antagonist [IL-1Ra] that is available for RA as monotherapy or combined with conventional DMARDs. It can be

used in selected patients with resistant acute gouty arthritis. Canakinumab is a monoclonal antibody against IL-1β with a longer half-life than anakinra that is used in autoinflammatory conditions and acute gout with limited treatment options [35]. Rilonacept is a human IgG1 antibody that binds IL-1β and is used mainly in rare autoinflammatory conditions [36].

6.4.4 IL-6 Inhibitor

IL-6 is primarily a proinflammatory cytokine with some antiinflammatory effects which plays a role in rheumatic diseases. It activates B cells, T cells, macrophages, and osteoclasts and is a primary mediator of the acute phase response. IL-6 in combination with TNFα and IL-1 stimulates VEGF and metalloproteinase production [37].

Tocilizumab is a humanized antihuman IL-6 receptor antibody of the IgG1 subclass that binds to soluble and membrane IL-6 receptor to prevent binding of IL-6 to its receptor and interferes with its cytokine activity [29]. It is available in some countries for RA, juvenile idiopathic arthritis, and Castleman's disease and is being investigated for use in giant cell arteritis.

6.4.5 IL-17 Inhibitor

IL-17, which is a key cytokine in the defense against extracellular bacteria, amplifies multiple cytokines and stimulates neutrophils, macrophages, fibroblasts, synoviocytes, and keratinocytes that are major players in the pathogenesis of immune-mediated diseases [37]. IL-17A enhances the expression of numerous chemokines, metalloproteinases, antimicrobial peptides, and other inflammatory mediators and sustains inflammation by stimulating both the innate and adaptive immune responses [38].

Secukinumab is a fully human IgG1 monoclonal antibody against IL-17 that is available for psoriasis and psoriatic arthritis and ankylosing spondylitis, and is being assessed for uveitis associated with the latter condition [29]. It is administered subcutaneously monthly after loading doses. Secukinumab efficacy in RA is modest compared to the response in the other conditions [39].

6.4.6 IL-12/23 Blockade

IL-12 and IL-23 are pleiotropic cytokines that upregulate T cell responses. These cytokines, produced by macrophages and dendritic cells, role in the inflammatory cascade include promotion of NK cells activation, T cell differentiation, and

expansion of Th1 lymphocytes to produce TNF, IL-2, and IFN-¥ [40]. IL-23, together with IL-6 and TGF-β, promotes Th17 cells differentiation and proliferation [41]. IL-12 and IL-23 are markedly increased in plaques/tissues of psoriasis and psoriatic arthritis.

Ustekinumab is a human IgG1 monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23 to interfere with binding to their cell surface receptors [29]. Besides inhibition of NK cell and CD4+ T cell activation and differentiation, it also interferes with the expression of MCP-1, TNF-α, IFN-inducible protein, and IL-8. Ustekinumab is available for the treatment of moderate–severe psoriasis and psoriatic arthritis by subcutaneous injection every 12 weeks after loading doses.

6.4.7 Costimulation Blockade or T Cell Activation Inhibitor

A biologic agent has also been developed to target the costimulation pathway of T cell activation and function for use in RA and other rheumatic diseases. The control and regulation of T cell activation involves CD28 and CTLA-4 [CD152] through interaction with antigen-presenting cells and their ligands, CD80 and CD86 [38]. Abatacept is a soluble fusion protein comprising CTLA-4 and the FC portion of the IgG1 that provides costimulation blockade, and is available for use in RA and juvenile idiopathic arthritis [29]. It prevents the suppression of T-reg activity and increased T effector cell activation. Abatacept can be given by weekly subcutaneous injections or by monthly IV infusions after loading doses.

6.4.8 B Cell Inhibition and Depletion

B cells not only have a central role in antibody production but also present antigens to T cells, activate T cells, and upgrade the production of proinflammatory cytokines, such as IL-1, 4, 6, 8, 10, and 12, TNF-α, VEGF, and MCP. Thus, agents that deplete B cells [rituximab] or inhibit activation of B cells [belimumab] can be used to treat a wide variety of autoimmune and rheumatic disorders.

Rituximab is a chimeric IgG1 monoclonal antibody, used in rheumatic and lymphoproliferative disorders, that deplete CD20-positive B cells, promote apoptosis, and stimulate complement-mediated cytotoxicity but has little or no effect on autoantibody production [29]. It is used to treat RA, granulomatosis with polyangiitis, microscopic polyangiitis, other vasculitis, SLE, systemic sclerosis, non-Hodgkin lymphoma, and chronic lymphocytic leukemia [CLL]. Rituximab is usually administered as 2–4 IV infusions every 6 months or longer as needed. Other anti-CD20 monoclonal antibodies include Y-ibritumomab, ofatumumab, obinutuzumab, and ocrelizumab.

Belimumab is a mAb that binds to soluble B-lymphocyte stimulator [BLyS] to prevent binding and stimulation of B cells [28]. It is used to treat SLE and being

assessed for Sjorgren's syndrome by IV infusions every 4 weeks after loading doses [25].

6.4.9 Kinase Inhibitors

Small molecules from simple chemical compounds that are not proteins or biologics are used as kinase inhibitors to target receptor signal transduction. The Janus kinases [JAK] are cytoplasmic protein tyrosine kinases that mediate signal transduction from multiple cytokine [IL-2, -4, -7, -9, -15, and -21] receptors to the nucleus.

Tofacitinib is an orally active small molecule drug that inhibits JAK-1 and JAK-3 to modify the immune response that is used in active RA unresponsive to MXT and other conventional DMARDs [29]. Its activity appears to be comparable to TNF inhibitor and also has increased risk for infection and liver disturbance.

6.5 Infections Associated with Biologic Response Modifiers

Although BRMs have produced dramatic improvement in the lives of patients living with severe rheumatic and autoimmune disorders, they also can result in severe life-threatening infections with significant mortality. The risk of infection may vary with age, underlying disease being treated, comorbid conditions, type of agent and duration of use, need for surgery and presence of prosthesis. Randomized, controlled trials may or may not detect increased risk of infections or uncommon opportunistic infections with these agents because of inadequate sample sizes, limited duration of follow-up, and patient selection criteria. Hence data on infectious risk, rates of infection, and occurrence of unusual infections are best gleaned from a combination of sources including extended data collection post-trials, national registries, observational cohort studies, and case reports.

6.5.1 Infections in Pediatric Patients on Biologic Agents

The fundamental infectious risk of BRM in adults with autoimmune inflammatory disorders can be compounded by age, comorbid conditions associated with aging, and the disability related to the sequelae of chronicity of the disease. For instance, patients with chronic deforming RA may have increased risk of pneumonia, soft tissue infection, septic arthritis, postoperative and prosthetic joint infections due primarily to the deforming arthritis and inactivity. In addition, the underlying disease itself can contribute to the risk of infectious complications and patients with RA may have greater risk of infectious complications compared to patients with psoriasis treated with the same agents, dose, and duration. There is evidence that

serious infections occur twice as frequently in patients with RA compared to matched controls that may not be related to the treatment [42, 43]. Moreover, studies indicate that the aberrations in T cell homeostasis and function in RA may contribute to the autoimmune response as well as immunodeficiency in these patients [44]. The reduced capacity to generate new T lymphocytes may be similar to immunosenescence recognized with aging.

It is important to review the risk of infections with novel biological agents in children in order to delineate their hazard without the influence of aging and chronicity. However, the available data are much less robust than in adults. In the last 18 years, BRMs have become an important option for the management of juvenile idiopathic arthritis [JIA]. TNF antagonists were the first of the biologics to be used and proven to be effective in JIA. A review published in 2015, using data from different sources, assessed the infectious risk of various biological agents used for JIA in comparison to MXT [45]. The rate of serious infections was lowest for MXT, 0.67/100 patient-years [PYs], and significantly increased for all biologics. Interestingly, it was found that the risk of infections was not the same for all TNF inhibitors, with rates of infection associated with infliximab {IFX} [3.42/100 PY] and golimumab {GOL} [3.03/100 PY] were greater than etanercept {ETN} [1.2/100 PY] and adalimumab {ADA} [1.42/100 PY, and the T cell activation inhibitor, abatacept [1.33/100 PY]. The IL-6 inhibitor, tocilizumab, was associated with the highest rate of infections [8.62/100 PY]. In this study opportunistic infections and tuberculosis [TB] were rare but herpes zoster occurred frequently in most studies [45]. Similarly, in another systematic review of biologic-associated infections in pediatric rheumatology, serious infectious rates were somewhat greater for IFX and GOL than for ETN and ADA [46]. A recent cohort of pediatric JIA receiving BRMs reported increasing serious infections [overall 12.6%], with an incidence rate of 97.5/100 PY for GOL, 4.2 for ETN and 3.4 for IFX, and 2.1 for ADA [47]. This suggests that GOL therapy should be avoided.

A more recent study from Germany compared the risk of serious infections in JIA associated with the use of TNF inhibitors compared to MXT [48]. A total of 3350 children with 5919 observation years were included. The rate of infection was lowest for MXT [1.6/1000 PY] and greater for ETN [8.1/1000 PY] and ADA [9.7/1000 PY]. The risk of infection was increased with steroid use, longer disease duration, and higher disease activity, but overall the risk of serious infections with the biologics was low. Most of the infections identified were from common bacterial diseases: urinary tract infection, sepsis, pneumonia, otitis media, osteomyelitis, cellulitis, and gastroenteritis; and viral infections included herpes zoster, primary varicella, viral bronchitis, and undetermined viral infections. The German experience is similar to other reports with infections complicating anti-TNF agents, where common bacterial infections predominated. Opportunistic infections are reported less commonly but include listeriosis, disseminated histoplasmosis, and pneumocystis pneumonia [49]. A recent review has tabulated invasive fungal infections complicating TNFα inhibitors in children: PJP*, Histoplasma, Aspergillus, Cryptococcus, Blastomyces, Candida, Coccidioidomycosis, Mucormycosis, Sporotrichosis*, *Trichosporonosis,* and *Malassezia* infection; but the most frequently reported

invasive fungal infection appears to be histoplasmosis [50]. Tuberculosis reactivation is a recognized complication of anti-TNF therapy in adults but is very rarely reported as a complication in the pediatric population [49], where the endemic rate of TB is extremely low such as in high-income countries where biologic agents are used predominantly.

There are little data on other BRMs in the pediatric population other than for TNF inhibitors. In a review of the safety of biologic therapies in JIA published in 2015, it was concluded that ETN, ADA, and the IL-6 inhibitor [tocilizumab] safety profiles were highly acceptable and that the IL-1 inhibitor [canakinumab] and T cell inhibitor [abatacept] had shown excellent safety profiles up to the time of the report [51]. However, the review of infectious complications of various biological agents in JIA reported incidence rates of infection highest for the IL-6 inhibitor compared to TNF and T cell activation inhibitors [45]. Serious infections associated with abatacept in open-label extension study over 2.9 years occurred in 3.9%, including bacterial meningitis, pyelonephritis, herpes zoster, cellulitis, and dengue fever [52]. The B cell inhibitor, rituximab, is used for JIA patients with inadequate response to TNF inhibitors, vasculitis, and hematological/neoplastic disorders. In an open-label prospective study of 55 children with JIA treated with rituximab with follow-up for 96 weeks, 8 [14.5%] serious infections occurred [all pneumonia with 3 PJP] and 18 non-severe infections [53]. Thus, the limited data suggest that the B cell inhibitor may have a greater risk of infection than the other BRMs in children.

6.5.2 Infections in Adult Rheumatic Diseases Associated with TNF-Inhibitors

Initial randomized trials of anti-TNF agents [IFX, ETN, and ADA] did not report increased serious infections compared to MXT in adult RA [54]. However, from 1998 to 2001 70 cases of TB in patients receiving IFX were reported to the US Food and Drug Administration [FDA] Adverse Reporting System [55] and this later increased to 242 cases after 2003. The incidence of IFX-associated TB was estimated to be 24.4 cases/100,000/year in contrast to the background incidence of TB in RA of 6.2 cases/100,000/year or fourfold increase. In addition, disseminated disease and extrapulmonary TB were more common than disease in the community population. Increased prevalence of other intracellular pathogens was also recognized with TNF inhibitors by the turn of the century, such as histoplasmosis, cryptococcosis, listeriosis, and rarely aspergillosis [56]. By 2006, a systematic review and meta-analysis of serious infections from randomized, controlled trials in RA treated with anti-TNF agents [IFX and ADA] were published [57]. The pooled OR for serious infection was 2.0 [95% CI, 13–3.1] and for malignancy 3.3 [95% CI, 1.2–9.1], confirming an increased risk of serious infections and malignancies compared to standard therapy, usually MXT. The number needed to treat for serious infection to occur was 59 within a treatment period of 3–12 months. It was noted

from reviews that infections associated with TNF inhibitors occurred early in the course of therapy and were most commonly respiratory tract [including pneumonia and sinusitis], skin and soft tissue, and urinary tract infections; but TB reactivation, other opportunistic infections and reactivation of hepatitis B and C viruses and herpes group viruses were noted [58].

In a review of the US National Data Bank for Rheumatic Diseases longitudinal study, 16,788 RA patients were followed semiannually for 3.5 years and 749 patients were hospitalized for pneumonia, but only prednisone and leflunomide were associated with increased risk of pneumonia hospitalization and not the anti-TNF agents [59]. A more recent study compared the risk of hospitalized bacterial infections among US veterans with RA associated with different treatments. The most common infections were pneumonia [37%], skin/soft tissue [22%], urinary tract [9%], and bacteremia/sepsis [7%] [60]. The rates of hospitalized bacterial infections were comparable for abatacept [T cell inhibitor], rituximab [B cell inhibitor], and the TNF inhibitors. Infection risk was greater with concomitant use of prednisone >7.5 mg/day and those with the highest baseline inflammatory markers [C-reactive protein]. In RA patients with previous infection while on anti-TNF therapy a large retrospective study found continued biologic treatment with abatacept and ETN [TNF inhibitor] was associated with lower risk of subsequent infection than with IFX, another TNF inhibitor [61]. This is similar to a previous study, from the same group, which reported that IFX was associated with increased serious infections compared to ETN and ADA in patients with RA [62].

Although some studies and reviews concluded that anti-TNF therapy was not associated with increased risk of serious infections compared to standard DMARDs in RA [63], other large, systematic reviews conclusion differ. In a systematic review of 49 observational studies, between 2009 and 2013, Ramiro et al. found that TNF inhibitors had a higher risk of serious infection than DMARDs but less than twofold increase [64], which seems acceptable. Two large-scale meta-analyses [after 2013] of randomized controlled trials came to the same conclusion. Michaud et al. analysis included 44 trials and found an increased risk of infection with TNF antagonists, but greater with the mAbs than ETN, a TNF receptor fusion protein [65]. In a larger scale, systematic review of 106 trials, standard-dose and high-dose biologics were associated with increased risk of serious infections, OR 1.31 and 1.90, respectively, while low-dose biologics were not [66]. The absolute increase in serious infections compared to traditional DMARDs per 1000 patients treated ranged from 6 for standard-dose biologic to 55 for combination of biologics.

The largest body of data on the infectious risk of anti-TNF agents has been derived from studies and reports in RA patients and less information on other rheumatic conditions or other autoimmune diseases. In a longitudinal cohort study of 440 spondyloarthritis patients followed for 1712 PYs, DMARD treatment but not TNF inhibitors were associated with the risk of serious infection [67].

6.5.3 *Opportunistic and Specific Infections with Biologics in Rheumatoid Arthritis*

Serious opportunistic infections have been sporadically reported in RA patients treated with BRMs. A review of 70 trials [up to June 2013] that included 32,504 patients assessed this issue [68]. TNF inhibitors were used in 46 studies and other biologics in 25 trials, controls were mainly treated with MXT and low-dose prednisone [<10 mg] was allowed in all arms. BRMs overall increased the risk for opportunistic infections but to a small degree, 1.7 excess infections per 1000 patients treated [number needed to harm, 582]. Significant increased risk was noted for mycobacterial infections [OR, 3.73] and viral infections [OR, 1.91], mainly herpes group, but not for invasive fungal infections, PJP or VZV, although there were increased trends but with wide confidence intervals. Although there was no significant increased risk of opportunistic infection mortality, there was an increased trend [OR, 1.91] with 4 deaths related to the biologics and 1 in the control group. The infection-related deaths with the biologics were attributed to TB [2 cases], EBV-related hemophagocytic syndrome [1 case], and VZV reactivation complicated by bacterial sepsis; and the single death in the control group was related to PJP [68]. The risk for opportunistic infections with BRMs was greatest for long-standing disease and for patients with RA with a median duration >10 years [OR, 5.20], less risk for those with a median duration of 2–10 years [OR, 1.93] and not significantly increased in early disease. Opportunistic infections were more common in short-term studies and appear to be early events after initiation of biologic therapy. However, the author has seen a case of fatal HSV hepatitis with multi-organ failure in a middle-aged male with nondeforming seronegative RA treated with weekly MXT and ETN for 7 years[unreported].

Although it is well recognized that VZV reactivation [herpes zoster] is increased with aging and immunosuppression, the data on biologics have been inconsistent. Whereas reviews of randomized trials reported no increased risk of VZV reactivation [68], large prospective observational cohorts from the German and British biologics registers have reported an increased risk of herpes zoster with anti-TNF biologics [especially mAbs] than standard DMARDs [69, 70]. In the past 3 years, three reviews have addressed this issue. In one review of 28,852 RA patients, besides increasing age prednisone therapy >7.5 mg/day was associated with increased risk of VZV reactivation but the risk from biologic therapy was comparable to standard DMARDs [71]. Another review mainly compared the risk of herpes zoster with the different biologic agents. Steroids had a significant association with VZV but there were no significant differences among the biological agents [72]. A more recent review included patients with rheumatic and other autoimmune conditions and expanded the meta-analysis to include 40 randomized trials and 19 observational studies [73]. Herpes zoster was modestly increased with standard DMARDs [OR, 1.21; 95% CI = 1.15–1.28], greater with steroids [OR, 1.73; 95% CI = 1.57–1.89] and patients on biologics, especially non-TNF-α blockers [for all

biologics OR = 1.71; 95% CI = 1.11–2.64; but for non-anti-TNF agents, OR = 2.19; 95% CI = 1.20–4.02].

Tofacitinib, while not a biologic, is an oral Janus kinase inhibitor that modulates the cytokine signaling of cytokines essential for lymphocyte function and is used in RA. In a recent study from the USA, health plan data from 2010 to 2014 were collected from RA patients to compare the risk of VZV from patients treated with biologics and tofacitinib [74]. The rate of zoster associated with tofacitinib was approximately double that observed in patients treated with biologics, but the rates between TNF inhibitors and non-TNF inhibitors were similar. A previous review of 66 randomized trials and 22 long-term extension studies found that the risk of serious infections with tofacitinib was comparable to the biological agents [75]. This result is similar to another report of phase II, III, and long-term extension studies in patients with RA and the overall rate of serious infection with tofacitinib was 3.09 events/100 PYs [76].

Although a large comprehensive review of opportunistic infections in RA patients on biologics did not find an increased risk of serious fungal infections with biologics versus standard DMARDs [68], invasive fungal infections do occur occasionally that can result in fatality. In a study using administrative claims data of more than 30,000 patients on TNF inhibitors, 158 [0.51%] developed fungal or mycobacterial infections [77]. About half of these were fungal infections, including PJP, cryptococcosis, histoplasmosis, coccidioidomycosis, and blastomycosis.

Patients with RA frequently undergo total hip and knee arthroplasty and are at increased risk for postoperative infections, but the risk of increased infection posed by biologics is unclear. A recent large retrospective cohort study with propensity-adjusted analyses addressed this issue [78]. The study included 9911 RA patients who underwent hip or knee arthroplasty receiving various biologics and with or without MXT or different dosages of steroids. The risk of postoperative infection and prosthetic joint infections [PJI] was similar across biologics [even with MXT] but PJI was significantly greater with prednisone >10 mg/day. Unfortunately, the study did not include a non-biologic therapy group and thus could not address the role of biologics on postoperative infections. A previous study from the Dutch registry showed that patients with RA treated with biologics did not have a significant increased risk of PJI compared to those not on biologics [79].

6.5.4 Risk of Infections from Biological Agents in Non-rheumatic Conditions

Few studies have addressed the risk of serious infections associated with novel biological drugs in non-rheumatic autoimmune conditions. Psoriasis is a chronic immune-mediated condition that may require long-term systemic therapy [in severe disease] with conventional DMARDs such as MXT or steroids and more recently anti-TNF agents and IL-12/23 antagonists. The risk of infection with these BMR,

however, may vary according to the underlying disease and degree of disability. The most extensive study to date involved data from the Psoriasis Longitudinal Assessment and Registry [PSOLAR] which included 11,466 patients with psoriasis followed for 8 years, 22,311 patients-years [PYs] [80]. Rates of infection in the non-biologics groups were 1.05/100 PYs [without MXT] and 1.28/100 PYs [with MXT], and were 083, 1.47, 1.97 and 2.49/100 PYs in the ustekinumab [anti-IL-12/23], ETN, ADA, and IFX [anti-TNF] cohorts, respectively. Thus, the anti-TNF mAbs appear to double the risk of serious infections than non-biologic therapies. The most common types of infection reported were pneumonia and cellulitis, and risk factors included increasing age, diabetes, smoking, and history of infection. In a smaller Canadian multicenter study of 398 patients with psoriasis, adverse events resulting in the withdrawal of biologic therapy occurred in 22 [4.04%] and infections occurred in 5 [0.92%] with a single case of TB reactivation [81].

Inflammatory bowel disease [IBD] patients are commonly treated with standard immunosuppressive agents such as steroids, AZA, MXT, and cyclosporine but more recently with biological agents. Infectious complications are significant causes of morbidity and mortality which can result from the disease process itself [such as abscess from Crohn's disease] and surgical complications. The greatest risk of infections is related to the use of combined immunomodulating agents rather than a single drug and include viral [CMV, VZV, and EBV], bacterial [*Mycobacteria, Listeria*, and staphylococci], fungal [PJP, *Aspergillus*, *Candida,* and *Cryptococcus*], and protozoa [*Toxoplasma*] pathogens [82]. A recent systematic review of randomized trials published the infections risk in patients with IBD on biologics with some surprising results. The analysis included 49 studies with 14,590 patients and found a moderate increase in any infection, OR, 1.19 [83]. However, there was an increased risk of opportunistic infections [OR, 1.90] but not with serious infections, which appears to be lower than controls in studies with low-risk bias [OR, 0.56; 95% CI, 0.35–0.90]. In an earlier meta-analysis of 7000 IBD patients on TNF-α inhibitors, less than 1% developed opportunistic infections [0.9% versus 0.3% for controls, RR 2.05; 95% CI, 1.10–3.85], and these included TB [8 cases], HSV [8 cases], oral or esophageal candidiasis [6 cases], VZV [8 cases], CMV [2 cases], EBV [2 cases, and one case of *Nocardia* infection [84]. There have been 92 reported cases of PJP in IBD patients, 88% received steroids alone or with other immune modulators, and 44% used anti-TNF agents, usually in combination with steroids or other immunosuppressive drugs [85].

The French national registry had collected all cases of opportunistic infections over a 3 year period in patients with various inflammatory diseases on anti-TNF therapy. TB [69 cases] was the most common opportunistic infection and other infections [45 in 43 patients], included bacterial [33%] such as 4 listeriosis, 4 nocardiosis, 4 atypical mycobacteriosis; viral [40%] such as 8 severe zoster, 3 varicella, 3 extensive HSV, 4 disseminated CMV; fungal [22%] such as 5 PJP, 3 invasive aspergillosis, 2 cryptococcosis; and parasitic infections [4%] with 2 leishmaniasis [86]. Monoclonal anti-TNF antibody and steroid use >10 mg/day were independent risk factors but not soluble TNF receptor therapy. Table 6.2 summarizes the affected pathway and risk of infections with BRMs used in autoimmune conditions.

Table 6.2 Infectious risk of BRMs in rheumatic and autoimmune diseases

Class	Immune impairment	Risk of infections	Types of infections	Specific agents
Anti-TNF [IFX, ETN, ADA, GOL, CTZ]	Block inflam., granuloma	Moderate increase [OR = 1.59–1.90]	Serious infections, OIs	TB, PJP, histo, VZV, HSV, HBV
Anti-CD20 [rituximab, belimumab]	Deplete/inhibit B cells	Low increase	Few serious, rare OIs	TB, HCV, HBV, JCV-PML
Anti-IL1 [AKA, CKA, GKA, RLN]	Inhibit inflammasome	Moderate increase	Bacterial pneumonia, cellulitis, abscess, etc.	Rare TB, histo, Candida
Anti-IL5 [MPL, RLZ]	Inhibit eosinophils	Possible?	? Parasites	?Helminth
Anti-IgE [omalizumab]	Impair IgE function	Moderate increase	Mild parasitic	Helminth
Anti-α4-integrin [natalizumab]	Impair WBC CNS migration	Moderate increase	Respiratory, CNS	JCV, HSV, VZV
Anti-α4β7 integrin [vedolizumab]	Impair WBC adhesion	Moderate increase	Enteric, surgical	Bacteria
Anti-IL6 [TCL, STX]	Impair B/T cells activation, neutropenia	Moderate increase	OIs with 8 mg/kg, peritonitis	TB, PJP, VZV, bacteria
Anti-IL12/23 [ustekinumab]	Impair T cell response	Low	URTI, OIs with steroids	VZV, Listeria
Anti-IL17A [SKN, IKZ, BDL]	Affect innate/adaptive immunity	Minor increase	URTI, cellulitis, UT	Candida, VZV
Anti-B cells [rituximab, belimumab]	Affect B/T cell function	Moderate increase	OIs, PML, fungus	JCV, PJP, HBV

AKA anakinra, *ADA* adalimumab, *BDL* brodalumab, *CKA* canakinumab, *CTZ* certolizumab, *GKA* gevokizumab, *ETN* etanercept, *IFX* infliximab, *GOL* golimumab, *inflam.* inflammation, *MPL* mepolizumab, *IKZ* ixekizumab, *RLN* rilonacept, *RLZ* reslizumab, *SKN* secukinumab, *OI* opportunistic infection, *URTI* upper respiratory infection, *histo* histoplasmosis, *SXT* siltuximab, *TCL* tocilizumab, *TB* tuberculosis

Disease flares are relatively common during pregnancy in women with autoimmune disorders and immunosuppressive agents including BRMs are often used. The risk of infection has recently been assessed in pregnant women on immunosuppressive agents. In a cohort of 4961 pregnant women with RA, SLE, IBD, psoriasis, or ankylosing spondylitis on different immunosuppressive agents only 71 {0.2%} experienced serious infections [87]. There was no significant difference in the risk of serious infection between the users of different agents, but high-dose steroid was an independent risk factor.

6.5.5 Overview of the Infectious Risk of the Different Classes of Biologics

6.5.5.1 B Cell Inhibitors

B cell depletion and inhibition with rituximab or belimumab are used in autoimmune and lymphoproliferative disorders. The risk of infection depends on the underlying disease being treated, age, and associated comorbidities. A review of this topic was published in 2015 [88], and the findings are summarized herein. B cell therapy, data mainly with rituximab, appears as safe, or safer, than other biological therapies in rheumatic diseases with low odds of serious infections. Incomplete and transient B cell depletion and sparing of the plasma cell may account for the relative safety. Prolonged and more intensive therapy poses a greater risk for serious infection. Hypogammaglobulinemia can occur as a complication and persist after discontinuation and predispose to bacterial infection. Neutropenia is another complication observed in 2.5–3% of RA patients, increased to 20% with the treatment of ANCA-associated vasculitis, and 3–27% with rituximab treatment of B cell malignancies. Most patients with neutropenia recover promptly but severe infection with the need for granulocyte colony stimulation factor has been described. With respect to opportunistic infections, few cases of TB [6] and atypical mycobacterial infection [7] had been reported with rituximab and belimumab. HBV reactivation has been reported with rituximab-treated patients with RA and malignancy, sometimes fatal. HCV progression in rituximab-treated RA patients had been noted and increased viral load with stable liver enzymes is greater with rituximab than with anti-TNF therapy. The rate of herpes zoster is not increased with these therapies. JC virus [JCV], a polyomavirus that infects 80% of people and remains dormant in the body, reactivation rarely occurs in immunosuppressed individuals to cause life-threatening brain lesions, and is most commonly seen with the acquired immunodeficiency syndrome [AIDS]. The demyelinating brain lesions result in progressive multifocal leukoencephalopathy [PML] which has been associated with at least 14 patients with autoimmune disorders treated with rituximab [5/100,000 exposed patients] and two cases of SLE treated with belimumab [88]. Invasive fungal infections have also been rarely reported with these agents, including PJP [0.06–1.2%], cryptococcosis, histoplasmosis, and *Scedeosporium* infection.

6.5.5.2 IL-1 Inhibitors

Comprehensive reviews of infectious risk associated with different biological agents were most recently published by the European Society of Clinical Microbiology and Infectious Diseases [ESCMID] and the findings are summarized [89–91]. The IL-1 inhibitors, anakinra, canakinumab, gevokizumab, and rilonacept are used for rheumatic disorders, genetic periodic fever syndromes, and eosinophilic asthma. A recent placebo-controlled trial showed that one of these agents [canakinumab] was

effective in controlling and preventing flares in colchicine-resistant familial Mediterranean fever, TRAPS, and the hyper-immunoglobulinemia D syndrome [92]. Infections were the most frequent adverse events with only 12 serious infections which resolved with therapy [cellulitis, pneumonia, pelvic abscess, gastroenteritis, pharyngotonsillitis, and conjunctivitis]. No cases of opportunistic infection occurred. Overall review of available data [89] indicate that IL-1 targeted agents are associated with a moderate increase in the risk of infection, most commonly mild to moderate bacterial infections with occasionally fatal sepsis, *Staphylococcus aureus* bacteremia, and pneumococcal meningitis. Opportunistic infections were rarely reported and included a few cases of TB, atypical mycobacteria, histoplasmosis, *Candida* esophagitis, and visceral leishmaniasis.

6.5.5.3 IL-5 Inhibitors

IL-5 [eosinophil differentiating factor] inhibitors [mepolizumab and reslizumab] are mainly indicated for refractory eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, hyper-eosinophilic syndrome, allergic bronchopulmonary aspergillosis, severe atopic dermatitis, and eosinophilic esophagitis. Various published trials with IL-5 inhibitors have not reported an increased risk of infection but the number of patients treated has been limited. Theoretically, increased susceptibility to helminth infection may occur [i.e., strongyloides] but the number of exposed patients to these agents is probably miniscule.

6.5.5.4 IL-6 Inhibitors

IL-6 is a key cytokine in inflammation, immunity, and tissue regeneration and the inhibitors approved for clinical use in various autoimmune diseases are tocilizumab and siltuximab. The available data indicate that IL-6 targeted agents are associated with increased risk of infection similar to other biological agents such as the TNF inhibitors [89]. Higher risk of infection was noted with older age, previous exposure to anti-TNF-α inhibitors, underlying chronic lung disease, and chronic steroids. Neutropenia occurs at a higher rate than other biological agents and an increased risk of gastrointestinal perforation has been reported with tocilizumab in the USA. Opportunistic infections with this agent have been reported with doses of 8 mg/kg [0.23 episodes/100 PYs] and include TB, atypical mycobacteria infection, PJP, invasive candidiasis, and cryptococcosis. The risk of herpes zoster is similar to other biological agents and the experience in patients with chronic HBV and HCV is small.

6.5.5.5 IL 12/23 Inhibitor

Ustekinumab, which targets IL-12/23, is mainly used for psoriasis, psoriatic arthritis, and Crohn's disease. Randomized trails had not found a significant increase in the incidence of infections [89]. Compared to other biologics, ustekinumab had

been found to have low rates of infection, mainly of the upper respiratory tract. Opportunistic infections were occasionally reported primarily with concomitant immunosuppressive drugs and these include *Listeria* meningitis, *Candida* esophagitis, disseminated histoplasmosis, VZV reactivation, and two cases of active TB. Large surveillance data found the incidence of serious infection in psoriasis patients with ustekinumab to be lower than anti-TNF agents and MXT [80]. Although the risk of herpes zoster with this agent is low, 2.5% within the first year, VZV meningitis and multidermal zoster have been reported [89]. So far HBV and HCV reactivation and flares have not been a concern and PML has not been reported. Thus, ustekinumab use to date has not posed a serious infectious risk.

6.5.5.6 IL-17A Inhibitors

Therapeutic blockade of IL-17A with secukinumab, ixekizumab, and brodalumab has been used in psoriasis, psoriatic arthritis, and ankylosing spondylitis. Overall, the available data indicate that IL-17 targeted agents are associated with a minor increases in the risk for mild to moderate infection, usually upper respiratory tract infections, cellulitis, urinary tract and mucosa–cutaneous infections, especially easily treated moniliasis [89]. Occasionally, VZV infection has been reported.

6.5.5.7 Ig E Inhibitor

The immunoglobulin E-targeted agent, omalizumab, has been used for approved and off-label indications such as severe persistent asthma with an allergy to perennial aeroallergens, refractory spontaneous urticaria, severe atopic dermatitis, allergic bronchopulmonary aspergillosis, severe drug allergies, angioedema, systemic mastocytosis, and Churg-Strauss syndrome [89]. The major concern with this agent has been risk of increased parasitic infections. This agent has been used only in a few patients from tropical and subtropical countries with a high burden of parasitic infections. The current evidence derived mainly from industrialized countries suggests that IgE-targeted therapy may be associated with a moderate increase risk of mild to moderate parasitic infections.

6.5.5.8 C5 Inhibitor

Eculizumab is a humanized monoclonal antibody that targets complement protein C5 and is a novel agent for the treatment of complement-mediated disorders, such as paroxysmal nocturnal hemoglobinuria [PNH] and atypical hemolytic uremic syndrome, but has been used for antibody-mediated kidney transplant rejection. Based on its mechanism of action on late complement activation, it is not surprising that eculizumab is associated with a 10,000-fold increase risk of meningococcal infection, 1.5% incidence in controlled studies [89]. Meningococcal vaccination is

recommended before receiving this agent. In a recent report from the Center of Disease Control and Prevention [CDC], 16 cases of invasive meningococcal infections were identified in which 14 received at least one MenACWY vaccine dose [92]. Only four isolates typed as group Y and the remaining isolates were nontypable strains that are not associated with invasive disease and cannot be prevented with vaccination. Antibiotic chemoprophylaxis may be needed to prevent these infections and patients should be counseled to seek immediate care for mild early symptoms of infection. Immunization with Men ACWY and MenB should be given 2–4 weeks before starting eculizumab.

6.5.5.9 CTLA-4 Inhibitors

Monoclonal antibodies [ipilimumab and tremelimumab] targeting the cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] are immune checkpoint inhibitors being used in advanced melanoma. CTLA-4 is important in the regulation of T cell priming by dendritic cells and blockade promotes T cell priming and is not expected to increase the risk of infection [90]. Phase II clinical trials did not suggest an increased risk of infection. However, the immune checkpoint inhibition results in the upregulation of the immune system which is associated with a variety of autoimmune-related adverse events, including severe rash, colitis, pancreatitis, hepatitis, pneumonitis, nephritis, hypophysitis, and thyroiditis [93]. These reactions often lead to the use of steroids and anti-TNF agents to treat the immune reactions which then predispose to infections. In a retrospective study of 748 melanoma patients treated with ipilimumab alone or combination with another checkpoint blocking agent, 7.3% develop serious infections, including bacterial pneumonia, intra-abdominal sepsis, PJP, invasive aspergillosis, disseminated VZV, *Strongyloides stercoralis* hyperinfection, and *Clostridium difficile* colitis [93]. The major risk factor for infection was prior use of steroids and/or TNF inhibitors or combination with nivolumab. Thus, CTLA-4 blockade does not appear to lead to increased infection unless used with other immunosuppressive agents, just before or in combination.

6.5.5.10 PD-1/PD-L1 Inhibitors

Another key immune checkpoint that inhibits T cell activity in peripheral tissues is PD-1/ PD-L1 [programmed death ligand]. Activation of PD-1 results in a profound inhibition of CD+8 T cells effector functioning in clearing infiltrating tumor cells. PD-1 and PD-L1 targeted agents include nivolumab, pembrolizumab, and atezolizumab. These agents are used to treat several metastatic cancers including non-small cell lung cancer, melanoma, renal cell cancer, and others. Controlled trials did not reveal an increased risk of infections and this was not expected due to their mechanism of action in increasing T cell effector function. Similar to CTLA-4 inhibition the PD-1/PD-L1 blockade increases the risk of autoimmune reactions which leads to the use of steroids and other immunosuppressive agents [90]. Review of

data on patients with melanoma treated with these checkpoint inhibitors found cases of serious infections in 6.0%, including PJP and TB, primarily in patients receiving steroids and anti-TNF agents for autoimmune reaction or combination with nivolumab and CTLA-4 inhibitors [90]. However, several cases of TB reactivation have been reported with PD-1/PD-L1 blockade without immune adverse events or use of immunosuppressive agents that may represent a form of immune reconstitution syndrome, as the infections occur rapidly within 3 months after initiating the immune checkpoint inhibitors [93].

6.5.5.11 Lymphocyte Function-Associated Antigen 3 Inhibitor

Alefacept is a dimeric fusion protein that inhibits the activation and proliferation of T cells by blocking of lymphocyte function-associated antigen 3 [LFA-3/CD2 interaction], affecting CD4+ and CD8+ effector function. It was the first biological agent approved by the FDA for treatment of moderate to severe chronic plaque psoriasis but production was halted in 2011 for business reasons [88]. Long-term studies showed that 3% of treated patients develop mild to moderate infections, mainly respiratory tract infections and cellulitis but no opportunistic infections [90].

6.5.5.12 Adhesion Molecules Inhibitors

Natalizumab is a selective adhesion molecule inhibitor of the α4-integrin chain that blocks the translocation of activated leucocytes across the blood-brain barrier and is approved for the treatment of relapsing-remitting MS. Vedolizumab selectively targets the α4β7 integrin to inhibit mucosal adhesion cell molecule and is used to treat refractory UC and Crohn's disease [90]. Efalizumab prevents binding of T cells to the intercellular adhesion molecule-1 [ICAM-1], presents on endothelial cells, keratinocytes, and dendritic cells, was used to treat severe plaque psoriasis but withdrawn from the market because of high risk of PML [90].

Natalizumab in a cohort of MS patients treated in Canada was reported to modestly increase the risk of infection [adjusted hazard ratio, 1.59], but mostly upper respiratory tract infections [94]. However, as of June 2017, there have been 731 confirmed cases of PML in patients on natalizumab [95]. The risk of PML is influenced by several factors: JCV seropositivity, prior immunosuppressive agents [AZA, MXT, cyclophosphamide, anti-TNF agents, and mycophenolate mofetil] and the duration of natalizumab therapy. With prior immunosuppression the risk of PML is estimated to be 1 in 1000 and high-dose steroids may be associated with higher risk by impairing the immune surveillance of JCV [96]. An earlier report also noted 20 cases of CNS infection of herpes viruses in MS patients on natalizumab, 16 due to HSV and 4 to VZV [97].

Vedolizumab does not affect the CNS immune surveillance as lymphocyte migration across the blood-brain barrier does not depend on α4β7 integrin and no cases of PML have been reported with this agent [88]. Combined data from clinical

trials and cohort studies indicate that vedolizumab treated IBD patients experience a moderately increased risk of serious infections [mostly enteric and surgical site infections] compared to placebo, 4.3 versus 3.4 events per 100 PYs [98].

6.5.5.13 CD-19 and CD-20 Inhibitors

CD-19 targeted agents, blinatumomab, inebilizumab, and combotox, deplete normal B cells with subsequent reduction of IgG levels with hypogammaglobulinemia of 6% compared to 0.9% with conventional chemotherapy [91]. These agents are mainly used for acute lymphoblastic leukemia and B cell lymphoma. Compared to conventional chemotherapy, CD-19 inhibitors have not been associated with a significant increase risk of infection [91].

Anti-CD20 monoclonal antibodies affect the immune response by modulating B/T cell interactions and may have a selective effect on autoantibodies production and impair cellular immunity. These agents are used to treat CD20-positive B cell malignancies, aggressive autoimmune conditions, transplant rejection, graft-versus-host disease, and MS [91]. With respect to infectious complications, the largest body of data is with rituximab therapy. Pooled data and meta-analysis of rituximab therapy in lymphoma and RA did not show an increased risk of infection. However, a large population study in patients with immune thrombocytopenia showed the risk of serious infection was 2.6 times higher in subjects receiving rituximab than those who did not but steroids increased the risk by 3.8-fold [99]. Post-marketing data indicate that anti-CD20 agents can result in infections associated with impaired cellular immunity such as PJP, PML, disseminated zoster, HBV, and HVC reactivation [91].

Ocrelizumab is an anti-CD20 humanized monoclonal antibody that depletes immature, naïve, and memory B-lymphocytes approved for the treatment of relapsing-remitting and progressive MS [95]. In phase III trials of ocrelizumab upper respiratory infections were more common [10.9%] than placebo [5.9% but serious infection risk was similar [6.2% versus 5.9%] [89]. The anti-CD20 agents can cause late-onset neutropenia, 1–5 months after therapy in 5–15% of rituximab treatment. The overall data suggest that anti-CD20 agents are associated with a moderate increase risk of infection, including severe respiratory tract infection, HBV, HCV, and VZV reactivation [91].

6.5.5.14 CD52 Inhibitor

Alemtuzumab is a potent immunosuppressive humanized monoclonal antibody that produces lasting B and T lymphocyte depletion [89]. CD4+ T lymphocytes are depleted for an average of 61 months and CD8+ lymphocytes for an average of 30 months [95]. This agent is approved for the treatment of MS and refractory B cell chronic lymphocytic leukemia [CLL] and off-label it is used for lymphoma, graft rejection in organ transplantation, and graft-versus-host disease. The risk of

infectious complications is greatest in therapy for B cell CLL and kidney transplant and lowest for MS [89]. Alemtuzumab induces severe depletion of peripheral blood lymphocytes [T and B cells, especially CD4+] and the expected infectious risk is estimated to be similar to AIDS. CD4 lymphocytopenia [<220 cells/μL] have been reported months after the completion of therapy. The risk of CMV infection was increased in non-Hodgkin's lymphoma trials and PML has been reported when used in lymphoproliferative disorders but not in MS treated patients [93]. Reactivation of HSV and VZV was commonly found ion MS studies. Human papillomavirus [HPV] appears to be increased [2%] and isolated cases of listeriosis and TB were reported in MS trials [91].

6.5.5.15 S1P Receptor Modulators

Fingolimod, the first oral MS therapy approved, acts on sphingosine phosphate 1 receptors [$S1P_{1,3,4,5}$] and prevents egress of specific lymphocyte subset from lymphoid tissues, resulting in peripheral lymphocytopenia [90]. Naïve and central memory CD4+ and CD8+ T cells subsets are most affected but the effector memory T cells are increased. In the central nervous system [CNS], fingolimod decreases the percentage of CD4+ T cells with a reversion of the CD4+/CD8+ T cell ratio. Treatment in MS with fingolimod has been associated with mild skin and mucosa VZV and HSV infections, but severe infections have been reported including fatal primary varicella infection, two cases of HSV encephalitis and a case of VZV laryngitis and one case of VZV encephalitis [90, 95]. Other opportunistic infections reported with this agent include cryptococcal meningitis, PML, histoplasmosis, extensive molluscum contagiosum, HCV reactivation, atypical mycobacteria infection, and Kaposi sarcoma [95]. To date, 9 cases of PML occurred with fingolimod therapy, with an overall incidence of 1 per 18,000 treated patients but the risk may be higher in older age.

6.5.5.16 Ubiquitin Proteasome Pathway Inhibitors

Ubiquitin proteasome pathway is an essential component of the protein degradation pathway and inhibition results in the induction of apoptosis in cancer cell lines and selective T cell deletion [100]. The proteasome inhibitors [PIs], bortezomib, carfilzomib, and ixazomib, are used for treating multiple myeloma and mantle cell lymphoma [90]. Multiple myeloma patients have increased incidence of invasive pneumococcal infection, herpes zoster, and influenza even without the influence of chemotherapy or biologics [101]. Due to the depletion of T cells, the use of PIs is associated with increased risk of reactivation of viral infections, especially VZV, and when used with other immunosuppressive agents [steroids] there may be enhanced risk of opportunistic infections [102].

Clinical trials and series have reported an increased incidence of zoster from baseline of 11–22.3% with treatment with bortezomib [103]. Since then most centers

have used prophylaxis with acyclovir or valacyclovir with subsequent trials with newer PIs [carfilzomib or ixazomib]. The risk of reactivation with CMV, HSV, and HBV with the use of the PIs appears to be low [90]. Trials with PIs have not reported an increased risk of pneumonia over comparator therapies [8% incidence], but occasional cases of PJP have been reported with combination with other immunosuppressive agents. Rare cases of nocardiosis and protothecosis have also been reported with PI treatment [90]. The severity of viral respiratory infections appears to be greater with the use of PIs. In Australia, influenza infection in patients on PIs resulted in high hospitalization [66.7%], intensive care [41.6%], and mortality [33.3%] [104]. Table 6.3 summarizes the risk of infection with biologics used for noninflammatory conditions.

6.6 Novel Non-biological Agents

Tyrosine kinase inhibitors reduce tyrosine kinase phosphorylation which is important in cell signal transduction, thereby inhibiting cancer cell proliferation [105]. Ibrutinib is a tyrosine kinase inhibitor that has been shown effective and approved by the FDA for chronic lymphocytic leukemia, B cell lymphomas, Waldenstrom macroglobulinemia, and refractory graft-versus-host disease. The main cellular target of ibrutinib is Bruton tyrosine kinase that is critical for B cell proliferation and can impair receptor-mediated phagocytosis, including phagocytosis of fungal organisms [106]. There have been several reports of opportunistic infections in patients treated with ibrutinib, including cases of PJP, cryptococcosis, and invasive fungal infections [107]. In a review of 378 patients treated with ibrutinib for lymphoid cancer serious infections developed in 43 patients [11.4%]: invasive bacterial infections in 23 [53.5%] and invasive fungal infections in 16 [37.2%] [108]. The infection resulted in the death of 6 of 43 patients [14%].

6.7 Prevention of Infections with Use of Biological Agents

Strategies to prevent serious infections and reactivation of opportunistic infections with BRMs include screening patients before starting therapy for latent TB [therapy for those positive], HBV [surface Ag and core antibody], HCV, VZV, and *Strongyloide*s in patients from endemic countries. Patients with HBVs-Ag or core antibodies [without protective surface antibody] should be treated with entecavir or tenofovir while on treatment with biologics. Patients with active HCV with detectable viral RNA should be offered curative antiviral therapy depending on the genotype. Subjects without VZV antibodies should be offered varicella vaccination and those with prior exposure may be considered for the new recombinant vaccine [Shingrix], which appears to be highly effective. Vaccination for pneumococci [Prevnar and Pneumovax] and meningococcal vaccines should be considered for

Table 6.3 Infectious risk of BRMs for hematological and neoplastic diseases and multiple sclerosis

Class	Immune impairment	Risk of infections	Types of infection	Specific agents
Anti-CTLA-4 [ILM, TLM]	None	With steroids/ anti-TNF for autoimmune reactions	Pneumonia, sepsis, OIs	PJP, VZV
Anti-PD-1/PD-L1 [NLM, PBL, ALZ]	None	With steroids/ anti-TNF for autoimmune reactions	OIs, pneumonia	MTB, PJP
Anti-CD19 [BTM, IBL, CMT]	Deplete B cells	Low	Bacterial	None
Anti-CD52 [alemtuzunab]	Depletes B/T cells	Probably high	Several OPIs	CMV, HSV, VZV, HPV, TB, Listeria
Anti-S1P [fingolimod]	Lymphocytopenia	Mild increase	Mild skin/mucosa occ. OIs, PML, crypto.	VZV, HSV, JCV, Histo., etc.
Anti-UPP [BTZ, CFZ, IXZ]	T cell depletion	Moderate increase	Viral, influenza, occ. OIs	VZV, severe flu, CMV, HSV, HBV

ALZ atezolizumab, *BTM* blinatumomab, *BTZ* bortezomib, *CFZ* carfilzomib, *CMT* combotox, *CTLA* cytotoxic-T-lymphocyte-associated antigen, *IBL* inebilizumab, *ILM* ipilimumab, *IXZ* ixazomib, *PBL* pembrolizumab, *PD-L1* programmed death ligand-1, *OI* opportunistic infection, *CMV* cytomegalovirus, *flu* influenza virus, *HBV* hepatitis B virus, *HPV* human papilloma virus, *Histo* histoplasma, *occ.* occasional, *MTB* Mycobacterium tuberculosis, *PJP* Pneumocystis jirovecii pneumonia, *UPP* ubiquitin proteasome pathway, *VZV* varicella zoster virus

certain biologics associated with increased infection with these organisms. Most guidelines do not recommend PJP prophylaxis for patients initiating biological therapy as the incidence is low, however, prophylaxis with cotrimoxazole may be considered for biologics which impair T cell function when used in combination with steroids or other immunosuppressive agents. Patients treated with the CD52-inhibitor [alemtuzumab] in trials and clinical practice were usually given PJP and herpes prophylaxis due to the high perceived risk. Patients being treated with BRMs should receive yearly influenza vaccine before or at the onset of the influenza season. Furthermore, they should be treated promptly with oseltamivir for respiratory symptoms as soon as possible until test [PCR] results are available.

6.8 Conclusion

Biological agents, that manipulate the immune responses, have been in use for the past two decades and their use is proliferating for a variety of diseases, including autoimmune inflammatory disorders, malignancies, organ transplantations, rejec-

tion, and graft-versus-host disease. Overall these agents have been found to be relatively safe in comparison to other treatments but with mild to moderate increased risk of serious infections with most of the agents. However, preventative steps can be taken to lower some of the perceived risks. Unfortunately, fatality does occur secondary to the use of these agents and this is especially devastating to the families and practitioners when used in non-life threatening conditions to improve the quality of life such as in psoriasis and RA. However, BRMs have improved the quality of life and life span [certain malignancies] for numerous patients.

Future research and development should explore developing novel agents that target selective pathogenic mechanisms of disease processes without affecting the protective component of the immune system. Another approach is to develop antigen-specific immunotherapies that reprogram or remove autoreactive cells and/or induce immune tolerance to self-antigens in autoimmune disorders [109]. Animal models of RA and SLE have demonstrated the feasibility of this concept.

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Chapter 7
Climate Change: Impact on Health and Infectious Diseases Globally

7.1 The Science of Climate Change

Palaeontological data indicate that the Earth has undergone major and catastrophic climatic changes within the past millions of years. Finding of fossils in the arctic of the precursor of crocodiles, dating back to the Cretaceous period when dinosaurs roamed the Earth, strongly support the presence of tropical or subtropical climate globally during this period. Geological scientists contend [based on strong data] that the Earth has undergone dramatic cyclical changes in temperature and climate for hundreds of millions of years. There have been at least five major ice ages in the Earth's history with periods of glaciation with advancing sheets of ice even to the equator and retreating with global warming every 40,000–100,000 years. It is believed that the planetary orbital cycles are the likely cause of the Pleistocene climatic cycles, but variations in atmospheric carbon dioxide are synchronous with global climatic change and in all likelihood played a significant role [Pleistocene Epoch, Britannica Online Encyclopedia]. There is scientific evidence that rapid global warming from volcanic emissions about 252 million years ago [end of the Permian Period] resulted in the mass extinction of at least two-thirds of marine and terrestrial animals [Erwin D. Extinction: How life on Earth nearly ended 250 million years ago. Princeton Univ. Press, 2015].

Discovery of climate change began in the early nineteenth century when scientists uncovered evidence of ice ages and natural changes of paleoclimate and greenhouse effect was identified [1]. Geologists found evidence of a series of geological ages with changes in climate by the late eighteenth century. Climate change is a significant and lasting change, from decades to millions of years, in weather patterns, and can be caused by different factors such as variation of solar radiation received by Earth, oceanic conditions [i.e., oceanic circulation], biotic processes, volcanic eruptions, and human-induced alterations of the world [1]. The current global warming and insidious but progressive climate change are attributed to human activities from

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increased generation of carbon dioxide [CO_2] to produce the greenhouse effect. It was recognized from the early-mid nineteenth century that the atmosphere transmitted the visible solar light waves efficiently to the earth's surface, then the absorbed light emitted infrared radiation [which is not transmitted efficiently by the atmosphere] and result in increased surface temperature. The outgoing rays of radiant energy are absorbed in the lower atmosphere to a much larger proportion than the incoming solar rays because they are mainly long-wave rays. An investigation then found that CO_2, water vapor, and methane strongly blocked the infrared radiation [blanket effect] and could result in increased surface temperature of the earth. By the end of the nineteenth century, it was proposed that changes in climate could result from variations in atmospheric CO_2 concentration and that human-induced generation of CO_2 could produce a greenhouse effect with global warming [1].

By the 1960s, increased levels of CO_2 and air pollution [smog] with rising temperatures were recognized to be a serious problem in many major cities of the world. In 1972, a review of the climatologic science concluded that anthropogenic [man-made] concentration and distribution of CO_2 greenhouse gas showed exponential rise, and accurately predicted the rate of global warming for the period 1972–2000 [2]. It was noted that the increase of 25% CO_2 by the end of the twentieth century corresponds to an increase of 0.6 °C in the global temperature, an amount greater than the climatic variation of recent centuries. Since the 1990s, numerous studies and models have confirmed the effect of anthropogenic greenhouse effect on climate change, attributed mainly to rising atmospheric CO_2 but included increased methane and chlorofluorocarbons to a lesser extent. In 1988, an international conference [consisting of hundreds of scientists] concluded that human pollution of the atmosphere represented a major threat to international security and was already causing harmful health consequences over many parts of the globe [3].

The effects of climate change with global warming continue to be experienced and realized in the twenty-first century with no end in sight. The Medieval Warm Period, which lasted from about 750 to 1150 years ago, was notable by warming of about 1 °C within the first 100 years, but the predicted warming of 1.4–5.8 °C for the period 1990–2100 is at a much faster rate experienced throughout mammalian evolution [4]. The trend of global warming continues to be highlighted in the popular press from dramatic changes noted across the world. New research indicates that of 1773 glaciers in the Canadian high Arctic 1353 shrank significantly between 2000 and 2016 and many are fated to disappear [B. Weber, the Canadian Press]. The average temperature climbed about 0.12 °C per decade until the mid-1990s, but from 1995 to 2016, the increase was 0.78 °C per decade [>sixfold increase]. The melting glaciers result in rising sea levels and land erosion with some tropical islands slowly disappearing and continents are losing coastal land as found along the Southern California coast, with prediction of 40 m of coastal land lost beyond the existing shoreline by the end of the century [D. fears, The Washington Post]. Current research suggests that global warming will lead to stronger hurricanes and cyclones with slower forward speed [resulting in longer exposure] and would generate an average of 24% more rain and result in more catastrophic floods [D. Fletcher,

Sun Sentinel]. Warm air holds more water than cold air and the warm ocean provides the fuel for hurricanes but may not result in more storms.

Many countries across the world are experiencing extreme heat in the summer and some countries are getting hotter at different times of the year. Even northern temperate countries are experiencing record high temperatures in the summer. Scandinavian countries normally have temperatures of 15–20 °C in the summer but are experiencing temperatures 10° above normal in the 30 s [J. Samenow, The Washington Post]. In the summer of 2018 cities and towns as far north as the Arctic Circle were experiencing temperatures near 90 °F [32.2 °C] and countries in Southern Europe [Spain and Portugal] had record high temperatures above 43 °C. Climatologist has noted that this kind of heat wave which used to occur once every 10 years is now occurring every 2 years [AJ Rubin, the New York Times]. Tropical and subtropical poorer countries will and are suffering the greatest from the increasing sweltering heat in the summer and aggravated by the humidity in the monsoon season. Countries and cities that are normally hot from March to September are getting hotter with temperatures rising commonly to 43–48 °C in the summer. In some major cities of India the heat index [average temperature and relative humidity] has risen by 0.6–0.69 °C in summer and 0.26–0.55 °C in monsoon seasons per decade between 1951 and 2010 [S. Sengupta, the New York Times]. Public health researchers found that a normally hot city [Ahmadabad] in western India experienced a 43% increase in mortality when the temperature rose to 48 °C in May 2010. Extreme heat is a major public health issue and is devastating the health and livelihoods of tens of millions of people. In Southeast Asia and many tropical countries, most days in the summer are too hot for physical labor outdoors. The World Bank recently reported that rising temperatures could decrease the living standards of 800 million people and by 2030 [the International Labor Organization estimate] could lead to a loss of $2.6 trillion in labor productivity [S. Sengupta]. In Japan, record temperatures were being reported in the summer of 2018 with 23,000 people hospitalized for heat-related illness in a week and 86 died of heatstroke [M. Rich, H. Ueno & M. Inoue, The New York Times].

7.2 Impact of Climate Change

Climate change can have a major impact on our well-being, livelihood, health, and the function of organized society. The direct effects of rising temperatures and global warming include change in the strengths of storms, more severe floods, and droughts and greater heat waves affecting the physical and mental health of populations across the world. The indirect effects include changes in crop yield with loss of income and increased risk of starvation in destitute regions depending on local agriculture, higher burden and distribution of some infectious diseases, and climate-induced population displacement and increased violent conflict [5–7]. Another effect of global warming, being experienced by temperate regions of the world [Europe and North America and Australia], is increased extensive wildfires with loss of thousands of hectares of forests every summer. Thus, worsening the green-

house effect by a massive release of CO_2 and other toxic products of combustion and causing extensive air pollution and, moreover, the loss of millions of trees deprives the environment of the natural purification of trees, which remove CO_2 from the atmosphere and replenish it with oxygen. Many of these effects are already being experienced and will only get worse without mitigation efforts by all countries and the global community. Deterioration of our environment will eventually lead to the reversal of human progress in the last hundred years by undermining the social and economic progress and gains in public health.

The effect of climate change on human health can be affected by three means: direct, ecosystem mediated, and human institution mediated. The direct effects include heat-related mortality from greater number and intensity of heat waves and average temperature; rising frequency and intensity of floods and storms with effect on injuries, drowning, spread of water-borne diseases, mental sequelae, and damage to human communities [8]. Impacts of ecosystem-mediated effects include changes in frequency and distribution of vector-borne diseases and water-borne infections, undernutrition from crop failure and population displacement. Besides droughts causing crop failure, global warming has been estimated to result in at least 20% agriculture failure from proliferation of damaging plant insects. Human institution-mediated impacts on occupational health risks and breakdown of the public health system with wider community detriment.

7.3 Health Effects of Global Warming

Between 2000 and 2016, the number of vulnerable people exposed to heat wave episodes increased by about 125 million, with a record 175 million more people exposed in 2015 [9]. The effect of extreme heat on health varies from the direct heat of stress and heat stroke, worsening of preexistent heart failure, increased incidence of kidney injury from dehydration, exacerbation of breathing difficulty in people with chronic lung disease from air pollution and increased allergens, and precipitation of mental illness [10–12]. The elderly, young children and people with chronic lung, cardiovascular, and renal diseases are particularly vulnerable to heat waves, summarized in Table 7.1.

Weather-related disasters may also be an effect of climate change. In the past 20 years, 90% of all natural disasters worldwide were weather related [9]. From 2007 to 2016, the Emergency Events Database recorded a 46% increase from the 1990 to 1999 average of weather-related disasters, with an average of 306 disasters per year. The continent of Asia is most affected by weather-related disasters due to the population density, poverty, and extensive area. Between 1990 and 2016, there were 2843 weather-related events affecting 4.8 billion people and causing 505,013 deaths [9]. These weather-related disasters include droughts, floods, storms, wildfires, and extreme temperature events. With the current trend in climate, the 2015 Lancet Commission estimated that by the end of the century there will be an additional 1.4 billion people affected by drought events and 2.3 billion affected by flood events

Table 7.1 Noninfectious diseases affected by climate change

Conditions	Effect of global warming/climate change	Outcome
1. Heatstroke	Direct effect of extreme ambient temperature	↑Elderly mortality
2. Heart disease	Extreme high temperatures	↑Heart failure
3. Chronic lung disease	Pollution/allergens and high temperature	↑Resp. difficulty
4. Kidney disease	High temperatures—dehydration	↑Renal failure
5. Malnutrition	Indirect effect of crop failure from drought/flooding In low-income countries	↑Children/poor
6. Melanoma	↑Sun exposure in fair-skin people	↑Incidence
7. Mental illness	Stress from climate-related disasters	Precipitate

Resp. respiratory

[13], which will result in an unimaginable toll of human lives. These events result in much more than event-related mortality, such as injuries, spread of diseases, food and water insecurity, and impact on mental health. Moreover, these disasters have long-lasting effect on housing, education, agriculture, safety, public health and health care infrastructure, and national economies—all which indirectly affect the well-being of the affected population. The mortality from weather-related disasters has increased in many countries including high-income countries. The death toll from natural disasters can be difficult to determine and is often underestimated, as the indirect impact on electricity, water supply, communications, and access to medical care are not included in the estimates. This is exemplified from the mortality in Puerto Rico after Hurricane Maria in 2016 and the official death toll was 64. However, later analysis including indirect consequences of the hurricane calculated that the excess death related to the hurricane was actually 70 times the official estimate [14].

Food security and undernutrition have a major impact on health and well-being. The most vulnerable countries with high levels of undernutrition are located in geographically climate-vulnerable regions, dependent on local production of food [9]. Increasing high temperatures have especially been found to reduce crop yields in lower latitudes. Rising temperatures have been shown to reduce wheat production by 6% for each 1 °C increase and 10% decrease in rice grain yield [15, 16]. The 30 most vulnerable countries for decreased production with climate change are located in Africa and Southern Asia which are low-income countries, highly dependent on regionally produced grains with minimal agricultural diversification.

7.4 Climate-Sensitive Diseases

The Global Burden of Disease Study [GBD] 2015 [13] listed and assessed 6 climate-sensitive diseases: diseases related to force of nature [weather-related events], heat and cold exposure related [heatstroke], protein undernutrition, diarrheal diseases,

malignant melanoma, dengue, and malaria [see Tables 7.1 and 7.2]. The main specific noncommunicable disease assessed was malignant melanoma with a direct link to ultraviolet exposure. Despite advances in treatment and surveillance melanoma mortality has been increasing steadily indicating increased incidence probably related to climate change [9]. The indirect effect of global warming on other diseases has not been systematically assessed. It is likely that hot temperatures curtail outdoor physical and exercise activity, especially in poor countries with limited air condition buildings, thus may predispose to a greater risk of diseases related to inactivities such as obesity, diabetes, hypertension, and cardiovascular disease and stroke. Globally, the incidence of obesity and diabetes has been increasing in nearly all countries [from low- to high-income nations], but the effect of climate change has not been assessed or considered.

7.5 Climate-Sensitive Infectious Diseases

Climatic factors are often implicated in the epidemiology of infectious diseases such as influenza outbreaks in the winter of temperate regions and monsoon season of tropical areas. The effect of climate change on infectious diseases epidemiology is complex and involves interaction with other factors, including socioeconomic, behavioral, demographic, topographic, and other environmental factors [9]. Most estimates of the effect of climate change on infectious diseases have focused on vector-borne diseases. However, infectious diseases may be sensitive to climatic conditions not only on their effects on proliferation and distribution of vectors such as mosquitoes and ticks, but also on pathogen survival outside the host, environmental contamination and water-borne diseases, alteration of natural immunity from malnutrition linked to droughts and floods, and disruption of the health care infrastructure from climate-related disasters such as hurricanes/cyclones. Although it is estimated that at least 50% or more of infectious diseases are affected by climate it appears to be an infrequent cause of disease emergence and mostly affects diseases caused by pathogens that spend part of their life cycle outside the host, exposed to the environment [17]. The most important diseases affected by climate are transmitted by arthropod vectors, water, and food.

7.5.1 Mosquito-Borne Infections

Mosquitoes are the most important and prevalent transmitters of vector-borne diseases, including malaria, dengue fever, yellow fever, West Nile fever, Zika virus, Chikungunya virus, filariasis, and others. These vectors are found worldwide except in regions permanently covered by ice. There are about 3500 species of mosquitoes and nearly three-fourths are present in tropical and subtropical regions and wetlands [18]. Mosquito-borne diseases are susceptible to climate change and are a major

Table 7.2 Infectious diseases affected by climate change

Mode	Disease	Microbe	Regions affected	Strength association
Vectorborne:				
Mosquito:				
Culex spp.	CNS disease	West Nile virus	Europe, North America	Good to strong
	Lymphatic filariasis	*W. bancrofti*	Parts of Africa	Projected increase
Anopheles spp.	Malaria	*P. falciparum*	Highlands of Africa	Weak, projected ↑
Aedes spp.	Dengue disease	Dengue virus	Europe, Medit. Basin	Good, projected ↑
	Zika/ Chikungunya	ZV, CGV	Americas, Europe	Weak, projected ↑
Ticks:				
Ixodes spp.	Lyme disease	*B. burgdorferi*	North America	Good, expansion
	Lyme disease	*B. burgdoferi* +	Europe	Good, ↑north
Ix. ricinus	Encephalitis	TBEV	Europe	Good, ↑north
Hyalomma spp.	MSF	*R. conorii*	Parts of Europe	Weak, ↑north
	CCHF	CCHF virus	Med. Basin, Iran	Weak, projected ↑
Other vectors:				
Sandfly	Leishmaniasis	*L. infantum/tropica*	Central Europe	Projected increase
Triatomine spp.	Chagas disease	*T. chagasi*	Reemerge in Chile	Fair-good,? ↑ in USA
Nonvector diseases				
Snails related	Schistosomiasis	*S. mansoni/ japonicum*	Africa, China	Projected increase
Waterborne diseases:				
Diarrhea	Viral enteritis	Rotavirus, norovirus, enterovirus	Anywhere with flooding	Fair good
Hepatitis	Outbreaks	Hepatitis A/E virus	Low-income regions	Flooding fair
Bacteria:				
Diarrhea	Outbreaks	*Vibrio cholerae*	Asia, Africa, South America	Good
		Campylobacter, E. coli, Shigella,	Flooding anywhere	Good
		Salmonella spp., *S. typhi*	Developing countries	Fair good

(continued)

Table 7.2 (continued)

Mode	Disease	Microbe	Regions affected	Strength association
Leptospirosis		*Leptospira* spp. outbreaks	Developing countries	Good
Melioidosis		*B. pseudomallei*	Southeast Asia	Fair good
Parasites:				
Diarrhea outbreaks		*Cryptosporidium* spp.	Flooding anywhere	Good
		Giardia spp.	Flooding anywhere [rare]	Weak
Miscellaneous diseases:				
Cellulitis		*Streptococci or S. aureus*	Warmer weather ↑risk for cellulitis in USA	Weak
Urinary infection		Coliforms mainly	Hotter days 6% greater risk of UTI in USA[a]	Weak
Surgical site infection		Various bacteria	Seasonal variability, ↑warmer weather	Weak
Coccidioidomycosis		*C. imitis*	Climatic factors affect outbreaks in USA	Weak
Hanta pul syndrome		Hantavirus	Weather factors, ↑rodents—Emergence in USA	Weak

CNS central nervous system, *ZV* Zikavirus, *CGV* Chikungunya virus, *TBEV* tick-borne encephalitis virus, *CCHF* Crimean Congo hemorrhagic fever, *MSF* Mediterranean spotted fever

[a]Simmering J et al. Urinary tract infection incidence is associated with recent environmental temperatures. ID Week 2018; Abstract 127

public health concern globally. Most studies and models, however, have reported on the effect of climate change on the distribution and expansion of dengue and malaria to temperate and previously non-endemic regions of the world. It is generally considered that diseases such as dengue, malaria, and yellow fever are restricted to tropical and subtropical regions of the world, but historical records prove otherwise.

Historical records indicated that a malaria epidemic afflicted Paris in around 1865 and a major epidemic occurred in the USSR in 1923, with five million people infected and 60,000 died [19]. By the end of the Second World War, 41.5% of the European population lived in malaria-infested areas but the disease was eliminated from Europe by the 1970s, with the exception of Turkey [19]. Elimination of malaria from Europe was attributed to a combination of draining of swamps, urbanization, and widespread spraying with the insecticide DDT [di-chloro-diphenyl-trichloroethane]. Malaria was also endemic throughout much of the USA in the late nineteenth and early twentieth centuries [20]. It is believed that malaria was introduced

in North America by African slaves in the sixteenth and seventeenth centuries. The incidence of malaria peaked around 1875 and more than 600,000 cases occurred in the USA in 1914 [20].

Dengue is endemic throughout most tropical and subtropical countries of the world and the regions of involvement appear to be expanding. A possible dengue pandemic occurred in the latter part of the eighteenth century with widespread distribution including an epidemic in Philadelphia in 1879 and outbreaks in the Mediterranean region [21]. The primary vector of dengue, *Aedes aegypti* mosquito, was eliminated from the Mediterranean basin by the mid-1940s.

Yellow fever also transmitted by *Ae. Aegypti* mosquito was brought to the Western hemisphere and the Americas by slave trade ships from Africa after 1492. At least 25 major yellow fever epidemics occurred in North America, several thousand people died from an epidemic in Philadelphia in 1793 and 20,000 fatalities occurred along the Mississippi River Valley territories in 1878 [History of yellow fever, Wikipedia Encyclopedia]. The last major outbreak in the USA occurred in New Orleans in 1905. Major outbreaks of yellow fever also occurred in Europe in the nineteenth century probably introduced by mosquitoes on ships from the Caribbean. Barcelona experienced outbreaks in 1803, 1821, and 1870 with 12,000 cases and 1235 fatalities in the last outbreak [Wikipedia]. Smaller outbreaks also occurred in other European port cities such as Saint-Nazaire in France and Swansea in Wales.

There is cumulative evidence that mosquito-borne pathogens are increasing in temperate climates, North America, and Europe, such as the West Nile virus, Chikungunya virus, Toscana virus, and Usutu virus [22–25]. There is a widespread prediction that rising temperature, combined with societal landuse and habitat changes will result in increase in mosquito population size, development rates, and per-host biting rate, resulting in increased incidence of mosquito-borne diseases. Many of the models used, however, to predict climate change and mosquito-borne diseases have significant shortcomings. A novel comprehensive model has been developed that appears to address most of the limitations of the usual epidemiological-statistical models previously used. This method uses a temperature-dependent, delay-differential equation model, which incorporates diapause and the differential effects of temperature on the duration of and mortality of each life stage and demonstrates the sensitivity of seasonal variation and inter-intra-annual changes in temperature [26]. This model supported the prediction of increased mosquito populations and risk of increased mosquito-borne infectious diseases in temperate climates, but did not incorporate the effect of rainfalls and humidity which should be considered.

7.5.1.1 West Nile Virus

West Nile virus [WNV] is one of the most widely distributed arboviruses with greater expansion in temperate regions of the Western hemisphere since the 1990s to become established as an endemic disease. WNV is extensively distributed throughout Africa, the Middle East, many parts of Europe and the former Soviet

Union, South Asia, Australia, and North America [27]. The spread of this disease may be attributed to a combination of factors, including globalization of travel and trade, a suitable endemic vector, and natural wildlife host and climate change. *Culex pipiens* is the main vector of WNV that is commonly found in temperate regions, including Europe and North America, and the native birds are the primary amplifying hosts. Many temperate mosquitoes, including *Culex* species, survive the winter through diapause [state of metabolic inactivity] of the inseminated females and the WNV can be maintained in the mosquito population by trans-ovarian transmission. Diapause mosquitoes can survive temperatures of 0–10 °C, thus milder winters allow survival of larger populations of over-wintering vectors. However, in very cold winters such [as in Canada and Russia] diapause mosquitoes are able to survive in warmer shelters provided by underground drainage and sewers. *Cx. pipiens* population thrives through much of Russia with winter temperatures of −4 to −22 °C while temperatures in diapause shelters ranged from −1.1 to −11 °C [28]. Since 2010, there have been yearly outbreaks of WNV in eastern and southern Europe, which have been related to elevated monthly temperature and high July temperatures were used as a predictor of WNV risk later on in the season [29, 30]. Other environmental factors in subsequent outbreaks included state of vegetation, water bodies [rainfall], and bird migration routes [31].

7.5.1.2 Dengue Virus and Other Mimics

Dengue virus, Zika virus, and Chikungunya virus are transmitted by *Ae. aegypti* and *Ae. albopictus,* which also transmit Yellow fever and Mayaro viruses [zoonotic pathogen endemic to forests of tropical South America]. The annual global cases of dengue fever have doubled every decade since 1990, an estimated 58.4 million cases in 2013 causing >100,000 deaths and 1.14 disability-adjusted life years [32], potentially attributable to climate change [33]. Trends in the global transmission of dengue by the vectors have been assessed by the mosquito vectorial capacity, generation of new inoculations [daily] from a currently infectious case. Investigation revealed a significant increase in vectorial capacity to transmit dengue by both vectors from the late 1970s compared with 1990 by 3.0% and 6.0% for *Ae. aegypti* and *Ae. albopictus,* respectively [9].

Both the incidence and geographic range of dengue have increased dramatically within the last 50 years. Prior to 1970, only nine countries experienced severe dengue epidemics and now the virus is endemic in >100 countries [34]. The prevalence of dengue has increased by >75% in the past decade [35] which arguably could be secondary to global warming, increased rainfall and spread of the vector. Future climate changes with increasing temperature and humidity are predicted to increase the incidence of dengue fever in tropical and temperate regions of the world [36–38]. Recent studies in India and China have also demonstrated that climate conditions of rainfall and temperature play key roles in the temporal relationship of abundance of mosquitoes, dengue transmission rate, and incidence in the population [39, 40].

Although *Ae. aegypti* is not established in Europe it has been implicated for occasional dengue outbreaks in Europe, including the epidemic of 2013 in Madeira, Portugal [41]. Increase geographic dispersion of *Ae. albopictus*, however, has occurred throughout Europe coinciding with favorable climatic conditions, trade, and travel since the last 30 years. The Asian tiger mosquito [pseudonym] is considered the most invasive mosquito and became established in Italy in 1990 and spread throughout the Mediterranean basin and neighboring countries [42]. The expansion of the mosquito coincided with climate change in France, the Balkans, the eastern coast of Spain and the Adriatic Sea, the Benelux countries, and western Germany [43]. Several vector-borne epidemics in Europe have been caused by *Ae. albopictus,* including autochthonous Chikungunya outbreaks in France and Italy in 2007, 2010, 2014, 2015, and 2017; and autochthonous dengue outbreaks in France and Croatia in 2010 [44]. *Ae. albopictus* and possible climate change was responsible for the local outbreak of 162 cases of dengue in the temperate metropolis of Japan [Tokyo] in 2014, the first outbreak in Japan in >60 years [Kobayashi D, et al. Dengue virus infection in *Ae. albopictus* during the 2014 autochthonous dengue outbreak in Tokyo metropolis, Japan. Am J Trop Med Hyg 2018; 98:1460].

Ae. albopictus tolerates a wider range of temperature variation and environment than *Ae. aegypti*, from tropical to temperate climate, related to diapause and other mechanisms [45]. Although *Ae. aegypti* is endemic in a few southern US states [Florida, Texas, and California], *Ae. albopictus* can be found in 36 states with its northernmost boundary below Canada in parts of New Jersey, southern New York, and Pennsylvania [46]. To date [in recent times] locally mosquito-transmitted infections of Dengue and Zika viruses have only been reported from normally warm southern states such as Florida and Texas [47, CDC, Update on noncongenital Zika virus disease, 2016], but it is predictable that they will expand further north in the more temperate regions if climate change is not mitigated. Surprisingly, no locally transmitted case of Chikungunya virus has been reported from US states even though the disease has become established in the Caribbean.

7.5.1.3 Malaria

Despite global efforts to curb malaria, the decline in the world's burden of malaria has stalled and there is evidence that in some regions there are signs of reversal in the gains achieved, arguably related to climate change. In 2016, there was an increase of five million cases from the previous year and 91 countries reported a total of 216 million cases, with 445,000 deaths [WHO, World malaria report 2017]. It is estimated by WHO that 80% of the global burden of malaria is maintained by 15 countries, all except one located in sub-Saharan Africa.

The vector for malaria parasites [*Plasmodium* species] is the Anopheles mosquito with 465 species and while 70 of these can transmit malaria, 41 species are the dominant vector for the transmission of *Plasmodium* parasite [48]. Anopheles species capable of transmitting malaria are found in 48 states of the USA [20]. *An. quadrimaculatus* and *An. freeborni* are the most important vectors in North America,

found east and west of the Rocky Mountains, respectively, but other species have been implicated in local transmission, *An. hermsi* in California [49]. Climatic conditions [ambient temperature, humidity, and rainfall] affect the life span of the female Anopheles and the completion of the sporogonic cycle [maturation of the parasite] in the mosquitoes. The sporogonic cycle of the *Plasmodium* depends on the species and the external temperature. The maturation cycle in the mosquito for *P. vivax* and *P. falciparum* is completed in about 8–13 days at 27 °C, but at lower temperatures it is considerably longer 20–30 days at 20 °C or 18 °C [50]. The cycle cannot be completed for these two species below 18 °C and transmission cannot occur and 33 °C is the upper limit for completion of the sporogonic cycle.

In a recent 5 year study from Botswana malaria transmission and the temporal relationships with climatic changes were assessed [51]. The malaria transmission pattern observed was similar in other sub-Saharan African countries. Rainfall, flood extent, mean minimum, and average mean temperatures showed a correlation with the incidence of malaria. In Zambia, the majority of the increase in prevalence of malaria between 2008 and 2010 was attributable to climate effects on transmission [52]. Projections of malaria spatial pattern based on climate-change model for South and Southeast Asia predicts a heterogeneous pattern. It is projected that malaria will decrease in India, southern Myanmar, southern Thailand, eastern Borneo, bordering region of Cambodia, Malaysia, and the Indonesian islands, while it is expected to increase in southern and southeastern China and Taiwan [53]. This is compatible with a study from China which projects a substantial increase in the exposed population to the four dominant malarial vectors in the future, 2030s–2050s [54]. In some districts of India fluctuation in climatic factors [rainfall, temperature, and humidity] is predicted to favor mosquito growth, parasite development, and malaria transmission [55].

There is much controversy whether or not climate change has affected the distribution and incidence of malaria, during a period when global malarial incidence has declined because of control measures. There is some evidence that warmer climate has allowed expansion of the vectors to the highlands of eastern Africa to allow malaria transmission. In recent decades, outbreaks of malaria have been reported from the mountainous regions of Kenya, Uganda, and Rwanda [48]. Modeling of spatiotemporal data at a regional scale in highlands of Colombia and Ethiopia indicate that climate change with warmer temperatures will, without mitigation, cause an increase of malaria burden in the densely populated highlands of Africa and South America [56]. There is also evidence that warm El Nino Southern oscillations are associated with higher risk of malaria and Rift Valley fever in the Horn of Africa and during the cold La Nina events greater dengue fever, chikungunya fever and yellow fever [57]. Another study of malaria transmission in Africa predicted a modest increase in areas suitable for malaria transmission but a net decrease in other areas [58]. The highest risk for transmission is projected to shift from coastal West Africa to the Albertine Rift between the Democratic Republic of Congo and Uganda and toward sub-Saharan coastal areas. Estimates of climate change on the African malaria vectors, *An. gambiae* complex, indicate that the vectors are shifting from West to East and South to areas where malaria has not been previously common [59].

The effects of climate change include not just rising global temperatures but increased frequency of extreme weather patterns, such as droughts, heavy precipitation, and floods. Between 2003 and 2012, approximately 50% of global disasters were related to extreme precipitation and floods [Brussels: Centre for Research on the Epidemiology of Disasters, 2014]. Large numbers of malaria deaths were reported after severe flooding in eastern Africa in 1997–1998 in Kenya and Uganda [60]. Heavy rainfall and flooding in Ugandan highlands in 2013 were associated with a 30% increase risk of malaria in the local population [61].

Reintroduction of malaria in temperate regions previously endemic for malaria is of concern with climate change, including areas of Europe and North America. In southern Europe, even though the vectors circulate only a few scattered autochthonous malaria cases have been reported from Spain and Greece [62]. Malaria was considered to be eradicated from North America by the 1950s, but from 1957 to 1994 74 locally acquired cases were reported from 21 states, including three northern states [Oregon, north-central New York, and New Hampshire] [63].

7.5.1.4 Lymphatic Filariasis

Lymphatic [Bancroftian] filariasis is a mosquito-borne parasitic disease endemic in 72 countries and listed as a Neglected Tropical Disease targeted for elimination by the WHO. There is little evidence that climate change has affected the epidemiology of the disease which has declined from 53 million infected individuals in 2000 to 29 million in 2016, attributed to annual mass drug administration [35]. However, the vector *C. pipiens* mosquitoes are susceptible to climate change and increase surface water from heavy rainfall and flooding could increase the risk of transmission. However, one projection from ecological niche modeling predicted that climate change and population growth will expand the range and risk of lymphatic filariasis in endemic Africa. It was estimated that the population at risk could rise from 543–804 million to 1.65–1.86 billion in the future depending on the climate scenario [64].

7.5.2 Tick-borne Diseases

The epidemiology of tick-borne diseases has been changing in recent decades possibly due to climate change. Whereas short-term climate changes [temperature and rainfall] can have effects on the mosquito life cycle and reproductive number of vector-borne pathogens, long-term climate changes are required to affect tick biology and pathogen transmission [65]. Ticks are responsible for the most diverse range of vector-borne diseases and are second only to mosquitoes as the most frequent cause of human vector-borne diseases. These arthropods parasitize every class of vertebrates in nearly all areas of the world and represent one of the most important mediators of zoonoses to humans [66]. There is evidence that there is a poleward [northern] expansion of ticks associated with warming climate, *Ixodes*

scapularis in North America and *Ixodes ricinus* in Europe [66]. The south-to-north dispersal of *Ixodes* ticks follows the migratory routes of birds facilitated by changes in the forest habitat. Normally hard-bodied ticks [*Ixodes* species] take refuge in the winter under the surface of the soil or litter of woodlands in temperate regions and undergo slow development. Harsh inclement weather would cause a die-off of most viable insects and milder winters would cause more abundant larval ticks in the spring.

The Center for Disease Control and Prevention [CDC] recently reported that the number of tick-borne diseases in the USA has more than doubled in the past 13 years [67], which in all probability is at least partly related to climate change. Lyme disease carried by *I. scapularis* in the northeastern USA and I. *pacificus* in the western states represents 82% of the reported cases, but others include *Ehrlichia chaffeensis, Anaplasma phagocytophilum, Rickettsia rickettsia,* tick-borne relapsing fever, *Babesia microti* and Powassan virus [North American tick-borne encephalitis]. The Powasssan virus is also transmitted by *I. scapularis* and the rise in cases [especially the northeastern USA] is associated with the expansion of the tick range. Lyme disease has increased in both incidence and geographic extent in the USA and Canada in the past two decades, which appears to be related to climate variables influencing the geographic distribution and abundance of ticks with other cofactors that drive the enzootic transmission of *Borrelia burgdorferi* [68]. It is estimated that *I. scapularis* has been detected in nearly 50% more US counties in 2015 compared to 1996 [69] and the burden of tick-borne diseases in the USA is greatly underestimated. Although CDC reports 30,000 cases of Lyme disease per year the true incidence is probably 10 times greater [65]. Data in Canada showed a geometric increase in a number of Lyme cases reported over 8 years, from 144 in 2009 to 2025 cases in 2017 [70]. Over 88% of the cases reported were from Ontario, Quebec, and Nova Scotia and the dramatic increase in Lyme disease is associated with an increase in abundance of the blacklegged ticks and the percentage of vectors carrying the pathogen. There is some but less robust data that climate change with warmer temperatures can increase the risk and range for Rocky Mountain spotted fever, plague, and tularemia in the USA [70–73].

In Europe, the primary vector for Lyme disease and tick-borne encephalitis, the two most important tick-borne diseases, is *I. ricinus* and *I. persulcatus* in Eastern Europe and Asia. Lyme disease accounts for the largest burden of tick-borne disease in the European Union with an estimated 65,000 cases per year [44]. There has been an increase of nearly 400% of reported cases of tick-borne encephalitis over the past 30 years, 2057 cases in 2014, in European endemic regions which could be related to increased surveillance, improved diagnosis and possible climate factors. *I. ricinus* is present throughout a large part of Europe with documented expansion to higher latitudes and altitudes, northerly in Sweden and higher elevations in Austria and the Czech Republic, and expansion in Norway and Germany [44]. High incidence of tick-borne diseases has been linked to moderate winters and warm, humid summers in Sweden, Slovakia, and Hungary and may be influenced by outdoor recreational activities. The risk of Lyme disease in Europe has been linked to warm winters, high summer temperatures, low seasonal temperature variation, and exuberant vegetation

[74]. With tick-borne encephalitis, the relative importance of climate change is more debatable, as other factors may play a role such as tourism activity, rodent host population density, socioeconomic conditions, and vaccination coverage [75].

The association of climate change and other tick-borne infections in Europe is unclear, although there has been expansion of Rickettsia in recent years and more suitable habitat for the spread of Crimean-Congo hemorrhagic fever [CCHF] in the Mediterranean basin [76]. Climate change is likely to expand the range of the vector [*Hyalomma marginatum*] northward of the Mediterranean Sea [76]. In Iran, changes in mean temperature, rainfall, and relative humidity have been associated with the monthly incidence of CCHF [77]. Thus with current trends in climate change, it is predictable that the burden of CCHF would increase in Iran. For the Mediterranean spotted fever [MSF], a 1 °C increase in mean maximum summer temperature has been correlated with a 32% increase in incidence in northern Sardinia, Greece [78]. The epidemiology of MSF in Spain and Portugal [79, 80] and southern France [81] appears to be associated with climate factors, increases with average higher temperatures and low precipitation and decreases with greater number of days with frost.

7.5.3 Sandfly-Borne Diseases

Phlebotomus species, blood-sucking sandflies, are the vectors of cutaneous and visceral leishmaniasis which are distributed in the Mediterranean region, South America, Asia, Southeast Asia, and Africa. They also transmit sandfly fever viruses and the geographically localized Carrion's disease in Peru due to *Bartonella bacilliformis.* The effect of climate variation has mainly been assessed for leishmaniasis in Europe and South America. The survival and reproduction rate of sandflies and parasite development are affected by temperature and relative humidity, thus climate change could affect the range and distribution of leishmaniasis in the future [82]. *Leishmania infantum*, responsible for visceral leishmaniasis, is endemic in the Mediterranean area and *L. tropica*, cause of cutaneous leishmaniasis, is episodically present in Greece and adjacent countries [44]. Although there is no evidence of increased leishmaniasis in Europe, climate change is likely to expand the range of sandflies to many countries of central Europe, the Balkan Peninsula, and the Carpathian Basin, but the expansion may be limited by the restricted flying-range of the insect [44].

Recent modeling studies in South America showed that with climate change the vector distribution will not uniformly expand. In Peru, a decrease in the distribution of sandflies in some concentrated areas but a northwest expansion is predicted [83]. Similarly in Brazil, modeling predicts one of the sandflies vector species shifting its range southwards in Brazil and Argentina [84]. Ecological niche models also predicted the expansion of suitable habitat for the sandfly vector, increasing the risk for leishmaniasis in presently non-endemic areas [85]. Several cases of locally acquired leishmaniasis in the USA had been reported and human exposure to leishmaniasis is predicted to at least double by 2080 in North America [86].

7.5.4 *Chagas Disease*

Based on data from 2010, it is estimated that about 5.7 million people in Latin America [recently estimated to be eight million people globally] are infected with *Trypanosoma cruzi* [87], the cause of Chagas disease and the most important human parasite in the Americas. Transmission of *T. cruzi* is mediated by the blood-feeding triatomine ["kissing bug"] infected feces contamination of abraded or bitten skin, mucous membranes, or oral ingestion. *T. cruzi* is endemic in Mexico, Central America, and most countries of South America with the highest prevalence in Bolivia. The triatomine bugs live predominantly in cracks and holes of huts and substandard houses and Chagas is primarily a disease of the poor and disadvantaged. The kissing bug can be found in the southern half of North America, including southern US states, large regions of Central and South America. It is estimated that there are 300,000 subjects with *T. cruzi* infection in the USA, primarily Latin American migrants, but 7 vector-acquired cases have occurred in the southern states since 1955 [88]. Many animals are reservoir hosts for *T. cruzi* in the USA, including woodrats, raccoons, skunks, and coyotes and 11 species of triatomine vectors are present in the southern USA [89]. Some counties in Texas are particularly vulnerable in low-income neighborhoods ["colonies"] with poorly constructed houses that provide suitable habitat for the insects and easy access into the homes [90].

The two major factors that have modified the epidemiology of Chagas disease in the last decades are climate change and migration patterns. In endemic countries, there appears to be a wider distribution of triatomine vectors and migration of Latin Americans have caused the emergence of Chagas in non-endemic countries through vertical transmission and blood transfusion or organ transplantation [91]. Recent studies have shown that a higher proportion of Latin American migrants are infected with *T. cruzi* than previously estimated [92]. Climate change appears to play a major role in the reemergence of Chagas disease in Chile. The distribution of the vector [*Triatoma infestans*] and *T. cruzi* correlated with the maximum temperature and the rainfall during the driest month [93]. The kissing bugs tend to feed more often to avoid dehydration when the temperatures are >30 °C with low humidity and shorter life cycle increase their population density and increase the chance of spreading the disease [94]. In some vector hosts [*T. infestans*], *T. cruzi* undergoes faster development with higher temperatures and this increases the risk of transmission [95].

7.6 Nonvector-Borne Diseases

There is a paucity of studies or projections on the effects of climate change on nonvector-borne diseases. Table 7.2 lists the nonvector-borne diseases already or projected to be affected by climate change.

7.6.1 Snails-Related Diseases

Snails are the key intermediate hosts for *Fasciola* and *Schistosoma* parasites and the local freshwater population is usually related to that of the parasites in endemic regions. The maintenance of the snail population is affected by water velocity, rainfall, and temperature, being most abundant at the start of the dry season in Nigeria with low rainfall and water velocity and moderately warm temperatures, with similar trend with the incidence of schistosomiasis [96]. Predictions based on risk modeling suggest a future decline of schistosomiasis in Northeastern Africa, but increased risk in Southeastern Africa with the chance of new endemic areas with warming temperatures [97]. In China, a modeling study projected similar trends with expansion northwards to currently nonendemic regions with an additional 8.1% of the area of China [98]. More recently, a systematic review of studies and models on the effect of rising temperatures on the ecology of intermediate snails and schistosome parasites came to similar conclusions, that climate change may profoundly increase the population size of snails, parasite density, and disease epidemiology [99].

7.6.2 Water-Borne Diseases

Climate change can result in extremes of weather besides warm–hot temperatures in different regions, from prolonged drought to heavy rainfall, flooding, and even increased risk of tropical storms and hurricanes. It is well established that floods and tropical storms often result in outbreaks of waterborne and foodborne infectious diseases, which range from bacterial, parasitic, and possibly viral gastroenteritis. This can result from overflow of the local sewage system with contamination of groundwater and treated reservoir water to destruction and inaccessibility of sanitary clean water systems. In a study from South Korea, the short-term changes in waterborne and foodborne infections were analyzed after 65 floods and typhoons over 8 years [100]. Compared with pre-disaster incidences, the incidences of *Vibrio vulnificus* septicemia increased 2.49-fold and shigellosis by 3.10-fold, but surprising typhoid and paratyphoid fever did not increase. This may depend on the local endemic rates and usual environmental degree of contamination. Massive cholera outbreaks are linked to natural disasters [after the earthquake in Haiti in 2010] and strife [war in Yemen 2017–2018] and should be expected with climate change-related hurricanes and flooding.

A comprehensive review has recently analyzed the impact of climate change in general on waterborne diseases [101]. From a review of 74 articles, higher temperatures were found to be associated with increased risk of diarrhea, more evidence for bacterial and viral pathogens than for protozoal pathogens [high confidence in the relationship]. The effect of droughts was found to be mixed and inconsistent on the risk of diarrheal disease, but in some instances, lack of clean potable water could lead to consumption of contaminated water with increased enteric infection. While there was heterogeneity in observed effects of heavy rainfall, there was a significant

overall positive correlation with diarrheal disease within a few days in both industrialized and developing countries, from a few cases to up to hundreds of thousands [101]. Most of the studies assessing the effect of flooding have reported increased diarrheal disease in comparison to preflood or non-flood periods in the same year compared to non-affected groups [high confidence]. Flood-related outbreaks were reported for cholera, acute watery diarrhea undefined, enterotoxigenic *E. coli*, rotavirus, and norovirus. In an earlier review, 87 waterborne outbreaks involving extreme water-related weather events were identified, with heavy rainfall and flooding accounting for about 55% of the events [102]. The most common pathogens reported in theses outbreaks were *Vibrio* spp. [21.6%] and *Leptospira* spp. [12.7%]. However, a wide spectrum of enteric pathogens has been reported, including viruses [2.5–25.7%], bacteria [89–93%], and protozoa [2.3%], mainly *Cryptosporidium* spp. Multiple pathogens were identified in 21.6% including hepatitis A [0.9–5.4%] and hepatitis E [0.5–2.7%] [102]. Waterborne pathogens can result from contamination of treated mains water, most commonly *Campylobacter* spp. and *Cryptosporidium* spp., or from environmental exposure. *Vibrio* spp. [cholera] outbreaks were most commonly reported from Asia, followed by Africa and South America.

Climate change is predicted to increase the burden of diarrheal disease in low-income countries by approximately 2–5% by 2020 with no additional risk to high-income countries [102], but these projections likely did not include events from unpredictable disasters from hurricanes and cyclones. One area of neglect that needs further study is the chemical contamination of drinking water after climate change-related flooding and disasters [103].

7.6.3 Miscellaneous Conditions

There are several infectious diseases that may be affected adversely by global warming and climate change, but the data are sparse and not systematically analyzed and the relationships with weather changes are weak and unclear. These include increased risk of cellulitis [104], coccidioidomycosis, Hantavirus outbreaks in the USA, leptospirosis, surgical site infections and urinary tract infections [105]. The outbreak of leptospirosis in Puerto Rico after Hurricane Maria is an example of flooding from climate change increasing the spread of infectious disease [106].

7.7 Prevention and Mitigation of the Effects of Climate Change

The Paris Agreement under the United Nations Framework convention on Climate Change aims to hold global mean temperature below 2 °C [limit it to 1.5 °C] above the preindustrial levels in this century [107]. The major mechanisms for implementation

are aimed at a significant global decrease in the use of fossil fuels [coal, oil, and gas], increase use of renewable energy sources [solar, wind, and hydro-energy] and reforestation or decrease in deforestation. Initially, most countries [180 of 197] signed on to the agreement but the goal is now in jeopardy with the withdrawal of the commitment by the present US regime, one of the largest producers of greenhouse gas. A recent analysis showed that policies to limit global warming by the end of the century could reduce dengue cases by about 2.8 million cases per year compared with a no-policy scenario that would increase warming by 3.7 °C [108]. Considering this is only one of the diseases affected by climate change, extrapolation from the study would indicate that policies to limit greenhouse gas burden and global warming could prevent tens of millions of diseases and probably save millions of lives.

Since the Paris Agreement in 2015, there has been some progress in recommended areas to mitigate or decrease climate change but these were modest and slow [9], and current pace and level appear inadequate to reach the intended goal. Besides addressing the root cause of climate change, other measures have been recommended by the 2015 Lancet Commission on Health and Climate Change and others to combat the projected increase in various diseases. A key component in an adaptation planning to counter projected increase of the many diseases, including national and coordinated global surveillance annually or biannually of vector-borne and waterborne/foodborne diseases. The list of adaptation planning by the Lancet Commission include (1) national adaptation planning for health; (2) city-level climate change risk level; (3) detection and early warning of preparedness for, and response to health emergencies; (4) climate information for health; (5) national assessment of vulnerability, impacts, and adaptation for health; (6) and climate–resilient health infrastructure [9].

Recent survey found that 30 of 40 countries reported having a national adaptation strategy for combating the adverse health effects of climate change, including the most vulnerable countries in Africa, Southeast Asia, and South America, but only 16 [40%] have implemented measures to increase the resilience of their health care infrastructure [9]. Thus, the majority of countries and especially the most vulnerable ones are not prepared to deal with increase infectious and other diseases with climate change. Mass drug treatment of neglected tropical diseases and maximum utilization of all vaccines available for preventable infections are measures that ameliorate the consequences of climate change.

7.8 Economic Impact

It has been estimated that extreme climate-related events between 2010 and 2016 have resulted in an annual average of $127-billion in global economic losses with 99% borne by low-income countries [9]. A recent study and projections estimated that if global warming were limited to 1.5 °C by the end of the century [UN target] the accumulated global benefit will likely [>60% chance] exceed US$20 trillion [109]. However, not all economic assessments have projected a major negative fiscal

impact of climate change. A recent report estimates that climate change will likely have a limited impact on the economy and human welfare in this century, with negative impacts mainly in poorer, hotter, and lower lying countries [110]. WHO estimates that globally, between 2030 and 2050, climate change is expected to cause approximately 250,000 additional deaths each year, with estimated direct damage costs to health care of US$2–4 billion per year [111]. Globally, health-related costs attributable to global warming from polluting fuels were US$5.3 trillion in 2015, more than the total spent on health by all the world's governments [112]. In 2009, climate change was "deemed the biggest global health threat of the twenty-first century" [113] and maybe it should be considered the biggest threat to the global economy as well.

7.9 Concern

In the first week of October 2018, an ominous report was released by the Intergovernmental Panel on Climate Change, which indicated that governmental policies alone are unlikely to achieve the target of limiting global temperatures to 1.5 °C above preindustrial levels, as set forth by the Paris climate agreement. This has put the onus on business and corporate leaders to do more and join in the efforts to limit climate change, a role they have neglected and historically have been complicit in the world's climate problem [S. Mufson, B. Dennis & C. Mooney; The Washington Post, October 15, 2018]. This requires creating entirely new industries to remove carbon dioxide from the atmosphere and overhaul the vast energy infrastructure. The UN report indicates that achieving the target of 1.5 °C target will cost an average of US$3.5 trillion a year through 2050, nearly a $1 trillion more than current pledges made by governments in Paris in 2015. Most of this money will have to come from the private sector and hopefully, businesses and corporations will wake up and heed to this urgent call.

A recent study also indicates that the earth atmosphere is warming quicker than estimated and that we have less time to limit global warming to the goal of 1.5 °C above preindustrial levels. The earth has already warmed 1 °C since the late nineteenth century. Research has recently shown that the world's ocean has been soaking up and retaining 60% more heat in recent decades than scientists realized [114], and the ocean is the main source of thermal retention in the climate system. A recent study using state-of-the-art climate model found that global and ocean warming led to the loss of oxygen from the ocean's interior, extending up onto the continental shelves, resulted in the mass extinction of animals and plants at the end of the Permian Period 252 million years ago [115]. Thus, the task of limiting global warming to less than 0.5 °C by the end of the century is daunting and requires unprecedented [so far uncommitted] actions by the global communities, governments, and private sectors.

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Chapter 8
Blood Transfusion-Associated Infections in the Twenty-First Century: New Challenges

8.1 History of Blood Transfusion

Research into blood transfusion began in the seventeenth century after William Harvey experiments on the circulation of blood and Richard Lower pioneered the first blood transfusion between animals in 1665 [Royal Society]; but the first blood transfusion from animal to human was carried out by Jean-Baptiste Denys in France [Blood transfusion—Wikipedia]. The first successful blood transfusion was performed using a syringe by the British obstetrician James Blundell to treat postpartum hemorrhage in 1818. Subsequently, the first successful whole blood transfusion was performed to treat a patient with hemophilia in 1840 by Samuel Lane in London. Blood transfusions were avoided in the late nineteenth century because of severe reactions and high mortality.

It was not until 1901, after discovery of the three blood groups [O, A, and B] by the Austrian Karl Landsteiner, that blood transfusion became safer and led to the acceptance for modern treatment in emergency blood loss and surgeries [Wikipedia]. The first blood transfusion for surgery was performed in 1906 at Case Western Reserve University in Cleveland. The First World War was the stimulus for the rapid development of blood banks and transfusion techniques, and the world's first blood donor service was established in 1921 by the British Red Cross. The first blood bank was established in a Leningrad hospital in 1932 and the US government established a nationwide program for blood collection in 1940 [Highlights of transfusion medicine history; http://www.aabb.org/tm/Pages/highlights.aspx].

Transfusion was recognized as a source of infection before 1941 with description of transfusion-transmitted [TT] syphilis and screening for syphilis in blood donors was instituted before blood banks became common. In 1943, Paul Beeson published the classic description of TT–hepatitis [Highlights of transfusion medi-

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cine history], but the malarial parasite may be the first microbe known to be transmitted by transfusion. Globally, it is estimated that 85 million units of red blood cells are transfused every year.

8.2 Adverse Effects

Transfusions of blood products are associated with several complications and most of these are due to immunological reactions or infections. The immunological reactions are more frequent than infections and include (1) acute hemolytic anemia [most often due to human error in cross matching of mismatch blood types]; (2) delayed hemolytic reaction >24 h to 28 days [usually due to low or undetectable anti-Rh and anti- Kid antibodies]; (3) febrile nonhemolytic reactions, one of the most common transfusion reaction that occurs in about 7% [due to release of inflammatory chemical mediators from stored white blood cells]; (4) allergic reactions caused by IgE anti-allergen antibodies from the donor or recipient [more common in patients with hay fever/allergies]; (5) rarely anaphylactic reactions, caused by IgA anti-plasma protein antibodies; (6) extremely rare post-transfusion purpura, associated with the presence of antibodies directed against both the donor and recipient platelets [human platelet antigen]; (7) transfusion-associated acute lung injury [similar to acute respiratory distress syndrome [ARDS]] within 6 h of transfusion, related to donor antibodies interacting with recipient tissue antigen with release of inflammatory cytokines resulting in capillary leakage; (8) and transfusion-associated graft versus host disease which occurs in immunodeficient patients whose body failed to eliminate the donor's T cells [Blood transfusion—Wikipedia]. A common non-immunological complication is transfusion-related circulatory overload within 6 h and acute respiratory distress with signs of heart failure.

8.3 Infections Associated with Blood Products

Blood products transfusion can cause infectious complications through three mechanisms: (a) transfusion of microbes present in asymptomatic donor blood [mainly viruses]; (b) contamination of stored blood products [primarily bacteria in platelets]; and (c) transfusion-related immunosuppression predisposing to postoperative infections and others. The risk of infection increases with the amount of red blood cell units or blood products transfused and patients requiring chronic blood or products are most vulnerable.

8.4 Transfusion-Transmitted Infectious Diseases

Despite the remarkable progress made in blood or blood products safety achieved in the last 30 years since the identification of the human immunodeficiency virus [HIV] and hepatitis C virus [HCV], concerns still abound with the risk of transmission from emerging infectious agents. For microbes to be transmitted by transfusion certain attributes are considered necessary: presence of the agent in blood during the donor's asymptomatic phase, the agent's survival/persistence in blood during processing/storage, and the agent must be recognized as responsible for a clinically illness/outcome in a proportion of the infected recipients [1]. A group of experts in 2009 [members of the AABB's Transfusion Transmitted Diseases Committee] identified 68 infectious disease agents capable of being transmitted by blood transfusion [1]. However, the list now is even larger and will keep expanding as the rate of emergence of new agents from 1940 to 2004 was 3–5 new viruses discovered every year, 60–70% from animal origin that can infect humans [2, 3]. The infectious agents were classified and prioritized on risk level based on combination of scientific/epidemiological assessment, public perception, and regulatory concern into red, orange, yellow, and white categories [1]. The list did not include the well-acknowledged transfusion-transmitted agents—HIV, HCV, hepatitis B virus [HBV], and *Treponema pallidum.*

Red agents have low to high scientific evidence of blood safety risk with the potential for severe clinical outcomes, including human variant of Creutzfeldt-Jakob disease [vCJD], dengue viruses [DENV], and *Babseia s*pecies. vCJD has a low to very low risk of transmission in North America [NA] but higher risk of transmission in the United Kingdom [UK] where it was first described. DENV has a low to very low [almost absent] risk of transmission in NA but moderate risk in endemic countries. However, *Babesia* has moderate risk for transmission in the USA but very low risk in Canada and Europe or countries where the parasite is not endemic. Orange category agents have sufficient scientific/epidemiological evidence of blood transmission risk that may support higher priority in the future. These include Chikungunya virus [CHIKV], potential risk as not proven transfusion transmitted; St. Louis encephalitis virus [SLEV], potential risk but not proven; *Leishmania* species low risk with blood transmission proven in possibly 10 cases mainly in endemic areas [4]; *Plasmodium* species are well documented with blood transmission, low in non-endemic countries and high in hyperendemic regions; *Trypanosoma cruzi* [Chagas disease] is well documented to be blood transmitted, low in the USA and Europe but moderate in South and Central America. Yellow category agents have low to absent risk of blood transmission, but there is public and regulatory concern. These agents include chronic wasting disease [CWD] prion agent, never detected in humans or donated blood; human herpesvirus-8 [HHV-8], transmitted by transfusion in Africa [5] and possible in the USA but not proven [6], and resulted in no clinical disease; HIV variants are potentially blood transmissible but never proven; human parvovirus B19 which has been proven to be transmitted by blood [four documented cases by 2009], but very low risk except for hemophilia and conditions

requiring recurrent chronic transfusion and immunosuppression; avian influenza A virus subtype H5N1 unlikely to be blood transmitted, but high profile for possible pandemic spread; simian foamy virus can be transmitted by blood transfusion in nonhuman primates, but never demonstrated in humans and is theoretically possible; *Borrelia burgdorferi* [Lyme disease agent] potentially possible but no proven cases of transfusion transmitted; and hepatitis A virus [HAV] is very rarely transmitted by transfusion in neonatal intensive care units. White category agents represent a watch list, subject to modifications with change according to circumstances. These agents include hepatitis E virus [HEV] which is documented to be blood transfusion transmitted in endemic regions and industrialized countries, mainly the zoonotic subtypes [7, 8]; and *Anaplasma phagocytocytophilum* which has been documented to be transfusion transmitted in the USA [8 cases by 2014] with potential for greater blood transmission due to high seroprevalence in some regions of the USA, unknown period of bacteremia, survival in refrigerated stored blood, and shown in animal models to be transfusion transmittable [1]. Since the AABB group publication in 2009, the list of agents was updated in 2014 with six new additions [9]. These included yellow fever viruses, miscellaneous arboviruses, XMRV, human parvoviruses other than B19, bocaviruses, measles virus, and MERS-CoV. Tables 8.1 and 8.2 lists the microorganisms recommended for screening donated blood.

8.5 Recent Trends in Transmittable Agents in Blood Donors

There is a strong correlation between the risk of transfusion-transmitted agents and the prevalence of endemic rate in the local population of the country or region. Hence epidemiological data on the prevalence of high-risk infectious microbes in blood donors can be used as a guide to assess blood transfusion risk in conjunction with other preventative measures. There is a marked regional variation in prevalence

Table 8.1 Screening for transfusion-transmissible infections

Mandatory screening			
Agent	Screening marker	Assay	Comments
1. HIV	Anti-HIV, p24 Ag, RNA	EIA, CLIA, NAT	Ag-antibody assays for all some countries NAT
2. HBV	HBsAg, anti-HBc, DNA	EIA, CLIA, NAT	HBsAg—all, anti-HBc—few NAT—some countries
3. HCV	Anti-HCV, HCV-Ag, RNA	EIA, CLIA, NAT	Anti-HCV—all, ant-HCV/-Ag-limited; NAT—some areas
4. *T. pallidum*	Anti-TP, aniti-reagin	TPHA, EIA, VDRL/RPR	EIA preferred; VDRL in high incidence countries

Data obtained from the World Health Organization [WHO], Geneva; 2009. https://www.ncbi.nim.nih.gov/books/NKB142989/

Ag antigen, *CLIA/EIA* enzyme immunoassays, *NAT* nucleic acid technique, *HBc* hepatitis B core

Table 8.2 Selective screening for specific blood-transmissible infections

Agents	Screening marker	Assay	Regions	Comments
1. CMV	Anti-CMV	EIA	None	Blood for immunosupp
2. Malaria	Parasite or Ag	Thick smear, EIA	Endemic, risk	Donor screening
3. *T. cruzi*	Anti-*T. cruzi*	EIA	Endemic	Migrants from endemic areas—screening
4. HTLV I/II	Anti-HTLV-I/II	EIA	Endemic	Some non-endemic areas
5. WNV	Anti-WNV, RNA	EIA, NAT	US, parts of Europe	Seasonal
6. HEV	RNA	NAT	Parts of Europe	Controversial
7. B19V	DNA	NAT	US, parts of Europe	Pooled plasma prod.

Data obtained from [126]
Ag antigen, *EIA* enzyme immunoassay, *NAT* nucleic acid technique, *immunosupp.* immunosuppressed, *prod.* products

of these agents and the data in recent years will be presented by country, but is incomplete from lack of recent studies from some regions.

8.5.1 China

In China recent data from 2008 to 2015 for blood donors screened for HIV, HBV, HCV, and syphilis from the southwest region showed a decreasing trend over the time period, from 2.39 to 1.98% [combination of the four agents], slightly lower than other regions [10]. Syphilis was the most prevalent, especially in females and farmers in rural regions. Since establishing the blood services, China had experienced several catastrophes with transfusion-transmitted diseases in the past, but since 1998 has undergone transformative changes in donor screening and donor testing. Donor selection is now voluntary donation with fixed groups and donated blood undergoes two rounds of testing with different equipment or reagents by different personnel [11]. Since 2010, nucleic acid test [NAT] was established in several blood centers and in 2015 the government invested for nationwide expansion of NAT. However, China's blood services do not screen for other agents, which are regionally endemic and can be transmitted by transfusion. A nationwide distribution of nine potential agents that could be targeted was recently reviewed. These infectious agents include *Plasmodium* spp., human parvovirus B19 [B19V], DENV, *Brucella* spp., severe fever with thrombocytopenia syndrome virus [SFTSV], *Leishmania* spp., HTLV, and *Coxiella burnetii* [Q fever] [12].

Despite malaria being endemic in some regions of China and previous reports of at least 87 cases transmitted by transfusion from 1992 to 2015 [12], the prevalence of malarial parasites in blood donors is unknown and screening of blood is not

performed. DENV is also endemic in parts of China and blood donors in 2014 from endemic areas in Guangdong province had IgM prevalence rate of 2.4% with one donor with RNA load of 944 copies/mL. Brucellosis is endemic in the farming communities of North China and the prevalence rate among blood donors from an endemic area [Xinjiang Province] was reported in 2015 to be 1% and *Brucella* DNA was detected in 0.39% [13]. SFTSV, a tick-borne bunyavirus, was first described in China concentrated in the mountainous rural areas in central-eastern China with episodic outbreaks from spring to autumn. No transfusion-transmitted cases has been described and the seroprevalence rates in blood donors were 0.54% from endemic area and 0.28% from non-endemic area, and two low-grade suspected viremic samples were detected by RNA testing [12]. HEV is found worldwide and many cases have been transmitted by blood transfusion all over the world [14]. Screening of blood donors from six urban blood centers in China was reported in 2010 as showing prevalence of anti-HEV IgG of 32.6%, anti-HEV IgM of 0.94%, and HEV RNA in 0.07% among 44,816 donations [15]. HTLV prevalence in China is low and the latest nationwide surveillance in blood donors reported a rate of 0.03% in 2014 [16]. *Leishmania* spp. can be transmitted by transfusion and the parasite can survive in human red blood cells [RBC] in storage conditions up to 15 days [17]. Up to 2010, there were 300 cases of kala-azar reported yearly from China, mainly from Xinjiang Province and other western provinces [12]. However, there are no surveillance studies in blood donors and no documented transfusion-transmitted cases in China. B19V has been documented to be transmitted by blood transfusion and can cause RBC aplasia in the immunosuppressed [18]. Among Chinese blood donors, the B19V DNA was detected in 0.58% but was 4.8% in the Tibetan population. However, B19V DNA was detected in 54.2% of plasma pools used to manufacture intravenous immunoglobulin, factor VIII, fibrinogen, etc. with viral loads of 1×10^2 to 1×10^7 gEq/mL, which is higher than recommended by the US FDA [1×10^4 gEq/mL] [12]. *C. burnetii* DNA has been detected in blood donated [0.3%] of seropositive donors of 12.2% during a large outbreak of Q-fever in the Netherlands [19], but blood donor screening has not been initiated in China. Q-fever is mainly endemic in Tibet, inner Mongolia, and Western China.

8.5.2 Africa

The threat of blood-borne pathogens is disproportionately high in Sub-Saharan Africa, but there is variation among countries. In Eritrea, 60,236 blood donors were screened between 2010 and 2016, and at least 3.6% of donated blood was positive for one of the acknowledged transfusion-transmittable infections [TTI], HBV, HIV, HCV and syphilis, and 0.1% for multiple infections [20]. The seroprevalence of HBV, HCV, HIV, syphilis, and co-infections were 2.0, 0.7, 0.3, and 0.6%, respectively. These rates are relatively low compared to other countries in Sub-Saharan Africa.

In Ethiopia, similar data was collected from 11,382 blood donors from 2008 to 2015 with overall seroprevalence of 6.6% of the TTI, and prevalence of HBV, HIV, HCV, and syphilis were 4.4, 0.6, 0.8, and 1.1%, respectively [21]. Higher prevalence of any TTI was reported in Eastern Ethiopia [11.5%] with the majority [94.5%] due to HBV [22]. In Western Kenya, the seroprevalence of the four TTI in voluntary blood donors was even higher at 9.4%, distributed among HIV, HBV, HCV, and syphilis at 1.15, 3.46, 3.21, and 1.56%, respectively [23]. Prospectively screened donors from 2005 to 2016 in Nigeria showed 14. 96% were infected with at least one of the four TTI with overall prevalence of HBV, HCV, Syphilis, and HIV of 4.1, 3.6, 3.1, and 4.2%, respectively [24]. However, the rate of all TTI declined significantly over the years with a remarkable decline in HIV. The seroprevalence of the four main TTI among blood donors reported from 17 different and reported between 2009 and 2016 was recently reviewed [25]. This study found that West African countries had the highest seroprevalence of the TTI than other countries, especially for HBV [10.0–14.96%] and HCV [1.5–8.69%], but HIV prevalence demonstrated declining pattern throughout the years. Blood transfusion-transmitted-associated HIV infection in Nigeria was previously reported to be responsible for 14 [2.3%] of 597 children infection between 2004 and 2011 [26]. The Western Cape Province of South Africa's blood supply appears to be exceptionally safe with the introduction of NAT since 2005 [27].

8.5.3 Middle East

The prevalence rate of the main TTI in blood donors appears to be lower in Middle Eastern countries than in Africa and Asian countries, with declining rates from 2004 to 2014 in Iran [28]. The overall seroprevalence rates of HBV, HCV, and HIV were 0.15, 0.1, and 0.004%, respectively. Similarly, low rates of TTI have been reported among blood donors from Jordan [29]. Data from Egypt in 2013 indicate that the prevalence of HIV and syphilis were extremely low [0%] but HCV and HBV were 7.2% and 2.3%, respectively, still posed a significant risk of blood transmission [30]. Recent prevalence data from Saudi Arabia among blood donors used serological testing and NAT from relatively small sample [3028] found: HBV sAg 0.33%, HCV 0.40%, HIV 0.13%, HTLV 0.20%, and HBV cAbs 9.81%; with additional detection by NAT.

8.5.4 Southeast Asia

Among blood donors from Pakistan [2014–2015] TTI was detected in 5.46% and 0.38% had multiple infections by rapid immunochromatographic technique [31]. The overall frequency of HCV, syphilis, HBV, malaria, and HIV was 2.62, 1.55, 1.10, 0.10, and 0.02, respectively. The prevalence rate of the TTI appears to be lower

in India with overall positive for any TTI among the donors 2.79% in Kolkata [32] and the cumulative seroprevalence in Darjeeling of HIV, HBV, HCV, and syphilis of 0.42, 1.24, 0.62, and 0.65%, respectively [33]. Another study from India reported that the prevalence of TTI was higher in replacement donors than voluntary donors, but overall decreased from 2008 to 2012 [34]. The prevalence of infection in donated blood has been decreasing in Thailand from 2010 to 2012 compared to 2007–2009, and rates up to 2012 for HIV, HBV, HCV, and syphilis were 0.26–0.28, 0.97–1.42, 0.26–0.42, and 0.35–0.53%, respectively [35].

8.5.5 South America

Seroprevalence data of the usual TTI in blood donors in South American countries are incomplete and only partially present for few countries within the last 5 years. In Brazil, NAT was introduced for HIV and HCV in 2012 and the prevalence of these two viruses was recently estimated to be 209.9 and 66.3 per 100,000 donations, respectively [36]. Argentina introduced NAT screening in blood banks for >10 years and reported positive donors for HIV at 0.075%, HCV 0.05%, and HBV 0.045% [37], which may represent intermediate risk in comparison between African countries and developed nations. Limited data from Colombia of 41,575 donors over a year note prevalence rates of: Chagas disease 0.49%, HBV 0.21%, HCV 0.45%, HIV 0.12%, and syphilis 1.68%, total prevalence of 2.95% [38].

8.5.6 Developed Countries

Most high-income industrialized countries have very low rates of the usual TTI in blood donors but recent updates of seroprevalence are only present for a few. Data from 14.8 million donations were collected from 2011 to 2012 in the USA, representing 50% of the blood supply [39]. Surveillance-positive rates per 10,000 donations were: HBV, 0.76 [0.00076%]; HCV, 2.0 [0.002%]; HIV, 0.28 [0.00028%]; and HTLV 0.34 [0.00034%]. The Dutch experience from 1995 to 2014 was recently updated and the prevalence of TTIs among blood donors was 6 to 60-fold lower than the general population [40]. New donors had higher rates of TTIs compared to repeat donors, and the prevalence rates of the TTIs from 2009 to 2014 per 100,000 donors were: HBV, 39 [0.00039%]; HCV, 16 [0.00016%], HIV, 2.4 [0.00024%], HTLV, 4.2 [0.00042%], and syphilis, 28 [0.00028%]. The prevalence of TTIs in the Dutch donor population was typically lower than in other industrialized countries where the rates varied from 32 to 136 for HBV, 31 to 82 for HCV, 1 to 4 for HIV and 1 to 10 for HTLV per 100,000 donors [40].

8.6 Risk of Transfusion-Transmitted Infections

The risk of TTIs is variable in different regions of the world and is dependent on several factors: prevalence of TTIs in the donor population, type of donors routinely used [voluntary, replacement, or paid], screening or deferral of donors, method of testing blood donated [serology, antigen detection, and NAT], and pathogen reduction techniques for treating donated blood. In general, industrialized countries use multiple methods, including NAT, plus with a low prevalence of the major TTIs have the lowest risk of TTIs. Poor or low-income countries, especially in Africa, with a higher prevalence of TTIs, less dependent on voluntary donation and lacking facilities for NAT have the greatest risk of TTIs. Whereas, middle-income countries [Brazil, China, etc.] have intermediate risks of the usual TTIs, see Table 8.3 for comparative rates of TTIs [41–44].

8.7 Risk of Blood Transmission of Specific Viruses

8.7.1 Cytomegalovirus

Cytomegalovirus [CMV] latent infection is very common in the adult population of industrialized countries [about 60%] and developing nations [>80%] and can be transmitted by blood, as it resides in leukocytes, once a person is infected indefinitely. Transmission of CMV does not pose a significant health hazard to the healthy adult or older child, but it can result in severe disease in the immunocompromised CMV-seronegative patients, i.e., stem cell transplantation and for premature neonates. Measures to reduce TT-CMV for high-risk groups include depletion of cellular blood products [leukoreduction] and selection of CMV-negative donations. Studies indicate that newly positive CMV-IgG donors pose the highest risk of transmitting CMV as their blood contains the highest levels of CMV DNA [45]. However, there is no scientific evidence according to a recent review that leukoreduction or any single strategy reduces the risk of TT-CMV infection in high-risk patients [46].

Table 8.3 Residual risk of TTI in various regions of the world

Agents	High income	Middle income	Low income	Comments
1. HIV	$\leq 0.33 \times 10^{-6}$	$\leq 11 \times 10^{-6}$	$\leq 64 \times 10^{-6}$	Depends on NAT
2. HBV	$\geq 0.16 \times 10^{-5}$ $\geq 0.16 \times 10^{-6}$	$\geq 289 \times 10^{-5}$	$\geq 534 \times 10^{-6}$	Depends on NAT
3. HCV	$\geq 0.03 \times 10^{-6}$	$\geq 191 \times 10^{-5}$	$\geq 207 \times 10^{-6}$	Depends on NAT

Data obtained from [43, 127, 128]
NAT nucleic acid technique
Note: High-income countries as exemplified by France; middle-income countries as exemplified by Brazil; low-income countries as in Sub-Saharan Africa, i.e., Gabon

8.7.2 Occult Hepatitis B

Transfusion-transmission of HBV is extremely low in developed and middle-income countries that screen blood for HBsAg and NAT, but a residual risk still remains from blood donors with extremely low viral DNA in the blood with occult HBV infection, that are intermittently shed from the liver or not detectable by even highly sensitive NAT. Models estimate a residual transmission risk of 3–14% with occult HBV donation after HBsAg and NAT non-reactivity [47]. Despite NAT testing for HBV, up to 2013 4–13 cases of TT-HBV infection occurred annually from occult or recent infection in the window period in Japan [48]. Individual NAT revealed that 1.94% of donations with low anti-HBc and anti-HBs titers were viremic. Since then the Japanese blood services had elected to discard all units with low anti-HBc and anti-HBs that accounted for only 1.3% of total donations [48]. A study from Australia [without universal anti-HBc testing] estimated that occult HBV residual risk was 1 in 982,000 units transfused which represented 55% of the total HBV risk, and was decreasing with individual NAT identifying repeat blood donors with occult infection [49]. Data from Brazil indicate that the presence of high anti-HBs titers [>100 mIU/mL] did preclude the presence of HBV DNA in the donor blood [50].

A recent study reported that 3 Slovenian blood donors with occult HBV infection infected 9 of 31 [29%] recipients with extremely low viral loads [51]. The study suggested that the minimal infectious dose should be revised from 100 to 16 copies [or 3 IU] of HBV DNA and that further prevention could be achieved by universal anti-HBc screening [performed by a few centers] or highly sensitive NAT able to detect 0.8 copies [0.15 IU/mL] or pathogen reduction methods.

8.7.3 Hepatitis E

Hepatitis E virus [HEV] is of worldwide distribution with >20 million cases each year in tropical/subtropical countries causing more than 56,000 deaths each year [52]. Endemic and epidemic diseases in these countries [Asia, Africa, Central America, etc.] are caused by genotypes 1 and 2 by oral–fecal route of transmission. But in Europe, North America, and parts of Asia [i.e., Japan] genotypes 3 and 4 are zoonoses present in many animals [especially domestic pigs] that cause sporadic infections by consumption of raw or undercooked pork but also by blood transfusion [53]. HEV viremic blood donors are usually asymptomatic with normal transaminase and donor screening interviews are not beneficial. Moreover, the asymptomatic HEV-viremia can be present for up to 68 days [54]. Although most infection with HEV causes asymptomatic or mild hepatitis, fulminant disease is seen in pregnancy and patients with preexisting cirrhosis and chronic hepatitis progressing to cirrhosis can occur in the immunosuppressed [53]. This is also of concern as organ transplant recipients and patients with hematological malignancy

more commonly receive blood or blood products transfusion, and immunocompromised patients develop chronic HEV in about 60% with infection [55].

HEV [genotype 1] transmission by blood transfusion was first described in an endemic area in 2004 [56], but since then most cases have been reported in industrialized countries with genotype 3. Cases have been reported from Europe [France, Germany, Spain, the UK], Australia, Canada, and Japan [57]. TT-HEV can occur with transfusion of RBCs, platelet concentrate, fresh frozen plasma, and pooled granulocytes. Presently, there are about 40 cases of TT-HEV with 21 from Japan and at least 17 cases of transfusion of HEV blood products not resulting in HEV infection [57]. Universal screening of blood products for HEV RNA is a very controversial topic in Europe and policies vary among countries. In 2012–2013 in England, 225,000 blood donations were retrospectively screened and 79 had detectable HEV RNA [1:2850], and follow up of 43 recipients showed 18 [43%] had evidence of HEV infection [58]. The prevalence of HEV viremia in blood donors vary from 1:762 in the Netherlands to 1:9500 in the USA, and the risk of viremic blood leading to infection was estimated to be 40–50% [59]. The risk of developing clinical infection in the recipient of viremic blood products may depend on the presence of antibodies, viral load, and volume of transfused blood. The minimal infective dose is unknown but low viral load <100 IU/mL has not been associated with HEV infection and the lowest inoculum known to lead to infection in the recipient is 2×10^4 IU [58]. HEV RNA screening of blood donations is now routinely performed in Ireland, the UK, and the Netherlands, but selective screening for use in high-risk patients is performed in some blood centers in Germany, France, and Switzerland [57].

8.7.4 Arboviruses

Arboviruses are of worldwide distribution with regional variation depending on the species. There is a significant risk of transmission by transfusion during the short period of asymptomatic viremia, especially during peak season with a high incidence of infection. However, it is often difficult to prove TT-arbovirus infection from vector-borne transmission in endemic regions. Although transmission by blood products had been proven only for a few arboviruses, there is a major concern since the Zika virus epidemic in the Americas 2 years ago. Infection with Zika virus is the most commonly asymptomatic and viremic donors could be easily missed. Moreover, TT-Zika to pregnant women could result in severe neurological fetal abnormalities [60].

Although Colorado tick fever virus was the first arbovirus reported to be transmitted by blood transfusion in 1975 [61], concerns of TT-arboviruses became a blood safety issue, not until the West Nile virus outbreak in the USA in 2002. West Nile virus causes asymptomatic infection in the majority of patients [about 80%], but the severe neurological disease can occur in the elderly and immunocompromised subjects. In the US outbreak, 16 blood donors were linked to 23 infected

recipients and all donors were negative for West Nile-specific IgM antibody at the time of donation [62]. The estimated risk of TT-West Nile virus during the epidemic period was 1.46–12.33 per 10,000 donations [63]. Since then yearly seasonal outbreaks [summer to fall] have occurred in North America but with decreased intensity. National screening by NAT was instituted in 2003, initially by minipool but after 2 years switched to individual donation, as one-third of RNA-positive donations were missed by minipool screening due to low-level viremia which can cause infection [64]. The estimated cost–benefit of West Nile virus screening in the USA in 2003 was $483,000 per quality-adjusted life year [65].

Other arboviruses shown to be transmitted by transfusion are dengue virus [DENV] and tick-borne encephalitis virus [66]. Despite high incidence of dengue fever in many tropical countries, annually at least 50 million globally, DENV has rarely been reported to be transmitted by transfusion. Up to 2016, there were only 5 well-documented clusters of TT-DENV infection [67]. However, a retrospective analysis of a large 2012 epidemic in Brazil was able to identify the 6th cluster of TT-DENV [68]. DENV-4 viremia was confirmed in 0.5–0.8% of donations during the epidemic and 42 DENV RNA-positive units were transfused to 35 recipients. However, 6 infections occurred in 16 susceptible recipients [37.5%]. Analysis revealed no significant association with transmission and viral load and 90% of donors and recipients had evidence of past DENV infection of one or more serotypes.

Chikungunya virus [CHIKV] is another arbovirus that results in clinical illness mimicking dengue fever, but results in more severe and persistent arthralgia and arthritis, and is widely distributed in the tropics with large outbreaks in the Americas and Caribbean in 2013–2014 [60]. CHIKV potentially can be transmitted by transfusion but there is no report of this occurring. CHIKV infection differs from DENV, Zika virus, and West Nile virus infections as most infected subjects are symptomatic and, thus, there is a lower risk of asymptomatic viremic donations. The risk of TT-CHIKV was recently assessed in a study from Thailand. The mean and maximal risks of viremic donations during an epidemic period was estimated to be 0.9% and 4.8%, but with only 10% asymptomatic cases, screening of donors could reduce the risk by 88.4% [69].

The rapid pandemic spread of Zika virus [ZIKV] since 2015 with reported cases in 85 countries and territories has posed the greatest risk for TT-arbovirus. Most viremic patients infected with ZIKV are asymptomatic and pose a threat to the blood supply in outbreaks and low endemic spread. Moreover, ZIKV produces severe teratogenic effects, can persist in whole blood up to 2 months [70] and four possible cases of TT-ZIKV have been reported from Brazil [71, 72]. During the ZIKV outbreak in the French Polynesia of 2013–2014, 42 of 1505 blood donors [2.8%] were positive for ZIKV RNA and only 11 subsequently became symptomatic [73]. Puerto Rico introduced NAT of donated blood in 2016 during an outbreak and ZIKV RNA was detected in up to 1.1% [74]. Similarly, NAT of asymptomatic blood donors in Martinique in 2016 detected ZIKV RNA in 1.8% and 54% reported symptoms 1–6 days post-donation [75]. In the mainland USA, more than 200 locally acquired cases of mosquito-borne ZIKV infection and >5300 cases of travel-associated infection have been reported [76]. As a consequence since August 2016,

all donated blood in the USA has been screened for ZIKV RNA. Over four million donations were screened with 9 confirmed positive [only on individual tested samples] for a rate of 1:480,654 donations [77]. ZIKV RNA levels in RBC varied from 40 to 800,000 copies/mL and detection up to 154 days after donation, but in plasma detected levels ranged from 12 to 20,000 copies/mL and detection up to 80 days after donation. The present plan of NAT of individual donors is projected to cost $137 million annually [78] and the cost-effectiveness of the blood donation screening exceed $1 million/quality-adjusted life-year [QALY] gained, which is about 10 times as high as costs considered appropriate in clinical medicine [79]. The current US strategy for individual NAT for ZIKV was more recently estimated to cost $341 million per QALY and screening was cost-effective only in the high mosquito season in Puerto Rico [80].

Ross River virus [RRV] is an arbovirus unique to the Australian region with confirmed cases of 5000 per year with the largest outbreak affecting 50,000 people in Australia, Papua New Guinea, and the Solomon Island and with recognized risk to the blood supply [81]. Like CHKV, RRV can cause epidemics of debilitating polyarthritis. The first case of TT-RRV was recently described, which prompted a comprehensive risk review. Modeling estimated the risk of infection in donors in Australia as 1:14,943 to 1: 95,039 and predicted 8–11 RRV-infected blood components issued in Australia during a 1-year period [82].

8.7.5 Other Viruses

Parvovirus B19 [B19V] infection is common in childhood and adulthood with seroprevalence of 30–40% in adolescents and 40–60% in adults, and more than 85% in the elderly population [83]. Many infected subjects are asymptomatic [approximately 25% of adults and 50% of children in outbreaks] or experience mild nonspecific viral-like illness [84]. Thus, blood may be donated during the period of viremia which occurs 1 week after exposure and lasts for about 5 days. An important pathogenic feature of B19V is the bone marrow cell tropism, especially erythroid progenitor cells, with increased susceptibility for infection with differentiation [85]. Transmission of B19V through blood products is feasible as high-level viremia regularly occurs during primary infection with $>10^{12}$ geq/mL in the early phase of acute infection of asymptomatic individuals [86]. B19V is frequently found in blood and plasma donations and is more commonly transmitted by pool plasma-derived products than RBC. Transmission via plasma-derived products can occur due to incomplete clearance of the virus from the blood, high-level viremia in acute infection, and the resistance of the B19V to most inactivation procedures used in preparing blood-derived products [87].

B19V is a frequent contaminant of blood and plasma donations and the virus DNA is most commonly found in blood products from multiple donors. B19V DNA is detectable in 50–80% of non-inactivated factor VIII concentrates and in 30–50% of solvent/detergent-inactivated IX concentrates [88]. High rates of B19V DNA

have been found in albumin [25%], immunoglobulin [IgG] preparations [20–75%], factor IX, and pooled plasma [>60%] with viral loads of 1×10^2 to 1×10^8 geq/mL [87]. Since no B19V transmission has not been documented from pooled-plasma products with less than 10^3 to 10^4 IU/mL B19V DNA, the US Food and Drug Administration [FDA] imposed a limit of 10^4 geq/mL B19V DNA from pooled plasma [87]. Cellular blood products are found to have B19V DNA in about 1% and RBC transfusion has been associated with the transmission of B19V primarily with high-level titers of $>10^7$ IU/mL [89]. However, a recent report from Japan described persistent symptomatic B19V infection with severe thrombocytopenia transmitted by RBC transfusion low levels of B19V DNA [1.0×10^4 IU/mL] [90]. Fortunately, most patients with TT-B19V are asymptomatic but the extent of clinical disease from transfusion transmission is unknown. The development of disease is influenced by the presence of hematological and immunocompromised disorders and the immune status of the host. Three groups of patients are at particular risk for serious disease with infection. Patients with chronic hemolytic disorders [i.e., thalassemia major, sickle cell disease] may develop transient aplastic crisis with acute infection; subjects with combined immunodeficiency syndrome can develop chronic severe anemia from bone marrow failure; patients with AIDS can develop pure red cell aplasia; and fetal abnormalities [hydrops fetalis] can occur in pregnant women [87]. Methods used to ensure safety of plasma-derived products include NAT of plasma minipools and individual donations and multiple steps of viral inactivation and removal with solvent/detergent, superheating at 80° C for 3 days, pasteurization, and nano-filtration [87].

Human T-lymphocytic virus types-1 and -2 [HTLV-1 and -2] are retroviruses that chronically infect lymphocytes that can be transmitted by transfusions, but only a small proportion of infected individuals will develop clinical diseases after many years. HTLV-1 infects five to ten million people worldwide from Africa, Asia, Caribbean, Central and South America and can cause debilitating spastic myelopathy, HTLV-associated myelopathy [HAM], and adult T-cell leukemia/lymphoma [ATL] [91]. HTLV-2 has not been linked with any specific disease entity but there is limited evidence that some affected patients may develop chronic neurological problems [sensory neuropathies, gait disturbance, bladder dysfunction, motor abnormalities, and mild cognitive impairment] and chronic lung infections and dermatitis [92]. HTLV-2 primarily occurs in the Americas, especially in Amerindians in North, Central, and South Americas [5–30% seropositivity] and in pygmy tribes of Africa; but the virus has been found in intravenous drug abusers [IVDA] in the USA and southern Europe [10–15%] [93]. Both HTLV-1 and -2 [primarily HTLV-1] have been shown to be transmitted by cellular blood products in Asia [first reported in Japan], Caribbean [Jamaica], and North America, but rarely recognized clinically [93]. A heart transplant recipient in France was reported to develop early signs of HAM within 4–5 months of TT-HTLV-1, the rapid onset most likely related to immunosuppression [94]. Two cases have been reported of ATL after TT-HTLV-1 in Taiwan in patients with pre-existing lymphoma and promyelocytic leukemia, 6 months and 11 years after the transmission [95]. Currently, many countries test for HTLV-1/2 antibodies in blood donors which may be cost-effective in high prevalence

regions, but its value in high-income low-prevalence countries that perform universal screening is controversial and debatable [93]. Using a mathematical cost-effective model, it has been estimated that testing all new blood donors for HTLV costs US $9.2 million per life saved, or $420,000 per quality-adjusted life-year gained, when the HTLV prevalence is 1 per 100,000 [96]. When the prevalence among donors is 10 per 100,000 the cost is estimated to be US $0.9 million per life saved, or $41,000 per quality-adjusted life-year gained. In many developed countries in North America, Europe, and Australia where the prevalence of HTLV-1 is less than 1 per million universal testing of donors does not appear to be cost-effective; yet in many low- and middle-income countries with much higher prevalence antibody screening is not performed [93]. Further investigation of filter leukoreduction and pathogen inactivation methods and their cost–benefit compared to antibody screening are needed to guide national blood collection systems.

8.8 Transfusion Transmission of Parasites

8.8.1 Malaria

The malarial protozoa, *Plasmodium* species, appear to be one of the first, if not the first, TT-infection described in 1911 [97]. The major four *Plasmodium* species [*P. falciparum, P. vivax, P. malariae, and P. ovale*] can cause TT-malaria, as they can survive in stored blood even when frozen [98]. The longest interval between exposure and transmission by donation was estimated to be variable by species: 8 years for *P. falciparum,* 5 years for *P. vivax*, 7 years for *P. ovale,* and 44 years for *P. malariae* [97, 98]. TT-malaria has been described in both endemic and non-endemic countries. The risk of TT-malaria is extremely rare in industrialized countries but still a major challenge in resource-limited endemic countries, especially in sub-Saharan Africa. In endemic countries, it is challenging to differentiate between mosquito-transmitted from TT-malaria and, thus, transmission by blood transfusion is frequently unrecognized and underestimated. Recent estimates indicate that TT-malaria is <0.2 cases per million in non-endemic countries to >50 cases per million in endemic countries [98]. Donors are asymptomatic and invariably semi-immune with low levels of parasitemia that can be missed on microscopy. Transmission is usually through whole blood or packed RBC but platelets and leukocytes seldom transmit malaria from RBC carry over.

Recent studies within the past 10 years demonstrated a high-risk TT-malaria in sub-Saharan countries with median prevalence of malaria parasites in donated blood by thick smears of 10.2% [range 0.7% in Kenya to 55% in Nigeria] [99]. Blood donors are not routinely tested for malaria in most malaria-endemic countries in Africa including Nigeria. In Pakistan, blood smear detected malarial parasites in 0.57% of healthy blood donors and in India the rate was 0.03% with rapid diagnostic tests confirmed with microscopy [100, 101]. Although non-endemic regions are

at very low risk for TT-malaria, this may depend on the proximity to endemic areas. In Brazil, malaria is endemic in the Amazon River basin and non-endemic in the extra-Amazon regions, i.e., Sao Paulo state. However, a recent study found that 7.4% of blood donors from Sao Paulo were positive for *P. falciparum* [5.14%] or *P. vivax* [2.26%] [102].

A recent review of TT-malaria in non-endemic regions reported 100 cases from 1911 to 2015 with only a few cases in the twenty-first century, the two most recent cases in 2015 were from the USA [103]. Fifty-four of these cases occurred in the American continent, 38 in Europe, 3 in the Mediterranean area, 1 in India, and 4 in Southeast Asia. The frequency of the different *Plasmodium* species was: *P. falciparum* 45%, *P. malariae* 30%, *P. vivax 16%, P. ovale* 4%, *P. knowlesi* 2%, 1 mixed infection with *P. falciparum/P. malariae*, and 1 case of an avian species *[Plasmodium praecox*] acquired in Greece. Fatal outcomes occurred mainly with *P. falciparum* [11/45] and rarely from *P. malariae* [2/30] or *P. ovale* [1/4] but the fatalities were not attributable to malaria [103].

Preventative measures taken by blood banks to avoid TT-malaria varies widely even in endemic regions and only a few countries in sub-Saharan Africa [Malawi, Sao Tome, Principe, and Sierra Leone] screen donated blood for malaria as of 2010 [98]. In non-endemic countries also varies with some countries [i.e., USA] rely on predonation questionnaire for potential screening and others [France, UK, and Australia] use antibody testing on donors considered at risk from preliminary questionnaire [103]. Screening of donated blood is most commonly by microscopy of blood smear or rapid diagnostic tests which are insensitive for low parasitemia, and serological tests cannot differentiate between remote and current infection. PCR is the most sensitive method but most endemic resource countries cannot afford this method for widespread use. Pathogen inactivation method using a combination of riboflavin as a photosensitizer with UV light device [Mirasol System for Whole Blood, Terumo BCT, Lakewood, Colorado] can reduces TT-malaria without damaging RBC [104].

8.8.2 Chagas Disease

Trypanosoma cruzi, the cause of Chagas disease, is widespread throughout rural Central and South America where it is transmitted by the triatomine bugs among the poor living in substandard houses. Severe cardiac disease occurs in 30–40% of chronically infected untreated individuals. TT-Chagas disease [CD] has been recognized in endemic areas for many years where screening of blood donors has been instituted [105]. With increased migration of Latin Americans to North America and Europe, TT-CD in non-endemic countries has become a concern. Transmission of CD was first recognized to be transmitted by transfusion in 1952 and the total number of TT-CD is estimated to be 300–800 in the last decades [106]. TT-CD in non-

endemic countries has been reported from the USA [*n* = 7], Spain [*n* = 5], Canada [*n* = 2], and Australia [106] and recently Switzerland [107].

Low-level parasitemia may be detected several years after infection in asymptomatic individuals in up to 50% of those infected and the parasite can survive blood storage at 4–22 °C and even freezing and thawing [106]. Cellular components of blood can transmit the disease but not plasma. Platelet transfusion is the most commonly reported blood products associated with TT-CD probably because of the higher parasitic load than other blood products [108]. Prevention of TT-Chagas includes universal or selective donor screening [questionnaire] and testing for *T. cruzi* antibodies. Blood donor screening in the USA was first instituted in 2007 for Chagas disease and as of December 2017, at least 2300 infected blood donors were reported from blood banks in the USA [CDC. Chagas disease surveillance activities—seven states, 2017. Weekly/July 6, 2018/67[26]:738–41]. Donor screening for Chagas disease in non-endemic countries includes: USA, Canada, Spain, UK, France, Switzerland, and Australia [106].

8.8.3 Babesiosis

Babesiosis is a zoonosis caused by an intraerythrocytic parasite, *Babesia* spp., most commonly *Babesia microti*, usually transmitted by *Ixodes* ticks and resembles the malarial parasite on the blood smear, but smaller. Babesiosis is most commonly reported from the Northeast and upper Midwestern USA, Europe and Asia Pacific including China. In immunocompetent hosts, it causes mild febrile illness, but severe disease with significant mortality occurs in immunocompromised, asplenic, and elderly patients. TT-babesiosis was first described in 1979 in the USA and since then there have been over 200 cases related to transfusion described with mortality of about 18–19% [109–111]. Over 95% of the cases were due to *B. microti* but at least 3 cases were from *Babesia duncani* [109] and recently a case from Arkansas secondary to *Babesia divergens* from multiple RBC transfusion was described [112]. Babesiosis has been transmitted by RBC stored for up to 35 days and by previous frozen RBC and rarely by platelets [113].

TT-babesiosis in endemic regions of the USA is increasing and of a public health concern as screening donors for *B. microti* is not yet mandated or routinely performed. *Babesia* seroprevalence in blood donors in foci of New York has been found to be up to 4.3% and 3.0% along the coastal Connecticut [111]. In a study on screening donated blood from Connecticut, Massachusetts, Minnesota, and Wisconsin with serology and PCR for *B. microti*, 335 [0.38%] of 89,153 blood samples were confirmed positive with 67 [20%] PCR-positive [114]. Thus, screening of donated blood in endemic regions of the USA would decrease the risk of TT-babesiosis.

8.9 Bacterial Infection from Blood Transfusion

Bacterial infections represent the foremost infectious risk from transfusion of blood products. This is most commonly due to bacterial contamination during the processing or storage of blood products [direct effect], but there is increasing recognition of an indirect effect. Blood transfusion is associated with immunomodulation which may result in increased risk of infection. Leukocyte reduction of blood has been shown to reduce the risk of health care-associated infections [115]. In a recent review of health care-associated infection after RBC transfusion, restrictive transfusion compared to liberal transfusion strategy did not reduce the overall health care-associated infections, but reduced the risk of serious infections [116]. This was particularly significant for patients undergoing hip and knee arthroplasty as well for those with sepsis.

Bacterial contamination of blood products can be from the donor's skin [i.e., *Propionibacterium acnes* or staphylococci] or from the environment with a variety of bacteria: *Yersinia, Pseudomonas, Proteus, Escherichia coli, Klebsiella, Acinetobacter*, *and Serratia* [117]. Some investigations found *Yersinia enterocolitica* as being most common as the organism is capable of growing and multiplying at low temperatures. Septic transfusion reaction is most commonly from platelet rather than RBC transfusion. Estimated risk of blood products contamination with bacteria is 1 in 5000 for platelets and 1 in 30,000 for RBC [117]. There is recent evidence from the Netherlands that platelet concentrate stored in platelet additive solution is associated with fourfold increased risk of bacterial infections [118]. In the USA, approximately 2.2 million units of platelets are transfused yearly [2011 data] and over a 5-year period from 2009 to 2013, 13 fatalities from bacterial contamination of platelet products were recorded, 2.6 per year or ≈1.3 per million platelet transfusion [119]. Since then there does not appear to be any improvement, as 5 fatalities were recorded from a bacterial infection in 2015 [120]. *Staphylococcus aureus* accounted for the greatest number of deaths due to contamination in the preceding 5 years [5/18] and other bacteria associated with fatalities included: *Serratia marcescens, Klebsiella pneumoniae, Morganella morganii, Pseudomonas fluorescens, Acinetobacter species*, *and Enterococcus faecium.*

Studies on active and passive surveillance for bacterial contamination of platelets have been reported with the culture of platelet samples. In a study over a 7-year period [2007–2013], 20 of 51,440 platelet units transfused were bacterially contaminated [0.004%; 389 per million] and only resulted in 5 septic transfusion reaction [121]. In high-income countries bacterial contamination of platelets, though the most common transfusion-transmitted infections, ranging from 0.01 to 0.07% of platelet units, but the rates are much higher in resource-poor countries such as in Africa. The rate of bacterial contamination in whole blood or RBC concentrate in 7 studies from sub-Sahara Africa average 8.8% and platelet contamination is likely much higher [122]. To prevent bacterial contamination of platelets the US FDA

recommends enhanced bacterial testing or pathogen reduction/inactivation strategies or both. One system which combines ultraviolet A and amotosalen for broad-spectrum pathogen inactivation is approved in the USA and Europe [123].

8.10 Summary and Future Directions

Although the blood supply is safer than ever before, there are still major concerns with respect to transfusion-transmitted infections, especially with the advent of emerging infectious agents. Moreover, the situation in resource-poor countries, especially in sub-Saharan Africa, still remains a challenge to provide safe blood supply comparable to developed nations. Blood use has declined significantly in the past decade in the USA, between 2009 and 2016 the number of blood units collected and distributed by the American Red Cross decreased by 26% and predictions for 40% decrease by 2020, raises the issue of a crisis in the US blood system [124]. Blood is an essential medicine with no replacement likely in the foreseeable future and safer blood supply is paramount for public health planning.

Prevention of multiple infectious agents being transmitted by blood transfusion is very expensive, time consuming and cumbersome. Many of the blood donation screening measures exceed US $1 million per quality-adjusted life-year gained, which are 10 times as high as deemed appropriate in clinical medicine [125]. The key to a safe and affordable blood system is a universally applied pathogen-reduction system that can inactivate all or most viruses, parasites, bacteria, and prions that can be implemented by resource-poor and resource-rich countries alike. This would obviate the need for expensive screening by serology, NAT, and others. Several methods of pathogen reduction are already in use including Mirasol [TerumoBCT, Lakewood, Co, USA] using a combination of riboflavin and UVB light can be applied to RBC and platelets to reduce most TT-viruses including HIV, HCV, and HBV by 2.3–5.19 log reduction as well parasites and bacteria; INTERCEPT [Cerus Corporation, Concord, CA, USA] utilize amotosalen and UVA light has shown similar properties against viruses, bacteria, and parasites; THERAFLEX [MacoPharma, Lille, France] uses photochemical inactivation with different methods for plasma and platelets, has demonstrated efficacy against viruses and bacteria, but 2 cases of HIV transmission have occurred after treatment of plasma; solvents/detergents for treatment of plasma is very effective against a wide array of enveloped and intracellular viruses, bacteria, and protozoa and can be combined with filtration to improve efficacy; chemical alkylating agents are also under investigation [126]. Larger comparative trials are needed to find the most suitable technique that can be used for whole blood, RBC, platelets, and plasma, to prevent transfusion-transmitted infection in the future.

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Chapter 9
Mass Drug Treatment of Tropical Diseases: Is It Really Progress?

9.1 Introduction

It is estimated that over a billion of the poorest people in the world are afflicted by a group of chronic "neglected tropical diseases" that often coexistent and affect most of the populations at some time in 58 tropical countries [1]. The list of neglected tropical diseases includes over 30 bacterial, fungal, helminthic, parasitic, protozoan, and viral infections, with 13 being the highest burden (see Table 9.1). The countries most affected are located in Africa, Asia, Southeast Asia, Latin America, Caribbean, Middle East, and the Pacific Islands, predominantly in the rural communities. The World Health Organization (WHO) in 2012 declared the target to reduce the burden of these diseases and eliminate them as public health concerns by 2020 [2]. These diseases cause a high burden of morbidity and some mortality resulting in perpetuation of the cycle of poverty and economic oppression. The neglected tropical diseases (NTDs) as a group cause approximately 534,000 deaths annually [3]. A diverse consortium of government agencies, pharmaceutical companies, charitable foundations, and private donors committed to large amounts of funds and donated treatment through the auspices of the WHO for the control of 10 of these diseases, and eradication of Guinea worm, in the London Declaration on NTDs [4].

Attempts at eradication and elimination of human infectious diseases have been ongoing for over a century with limited success. Smallpox being fully eliminated and polio and Guinea worm are on the cusp of being eradicated. Eradication programs for malaria, yellow fever, and yaws have failed [5]. There are presently two methods being used to control or possibly eradicate NTDs: (1) intensified screening, diagnosis, and active treatment; and (2) mass drug administration of targeted communities/populations [6].

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Table 9.1 Most prevalent neglected tropical diseases not controlled by mass treatment

Disease	Status	Control strategy
Buruli ulcer	Endemic in 30 countries in Africa, SE Asia, and Americas	Early diagnosis, antibiotics, or surgery
Chagas disease	15 million of the poor in Latin America	Inadequate vector control of kissing bug
Leprosy	Persists in 122 countries, 200,000 new cases per year	BCG, early diagnosis and treatment
Leishmaniasis	12 million infected globally, visceral, cutaneous and mucocutaneous	Vector control, early treatment
African trypanosomiasis	<10,000 cases in western and Central Africa	Vector control, early treatment
Dengue fever	50–100 million/year in >100 countries	Vector control, vaccine limited use
Cysticercosis	Endemic in Asia, Africa, and Latin America 10–20% infections in rural Africa and S. America	Improved sanitation, pork inspection

9.2 Intensified Diagnosis and Treatment

The four diseases targeted for intensified disease management (IDM) by the London Declaration of NTDs include leprosy, African (Gambian) sleeping sickness, visceral leishmaniasis in the Indian subcontinent, and Chagas disease. Common features of these diseases are long uncertain incubation periods and unknown degree of transmission by asymptomatic carriers, and the frequency of asymptomatic versus symptomatic transmissions may sabotage the attempt to control these diseases primarily on case finding and treatment [6].

Leprosy was one of the first NTDs targeted for elimination as a public health problem and although rates have declined, the target is far from being achieved as limited progress has been made in the past decade [7]. The current strategy for control includes passive case detection in health care centers, active case detection in mobile facilities ("skin camps"), and active case detection in high prevalence communities and households [6]. Early case detection and means of diagnosing asymptomatic carriers are needed, as diagnosis is mainly based on the presence of symptoms and signs. More sensitive diagnostic tools are needed, in conjunction with tracing and screening of contacts and institutions of preventative chemotherapy could reduce the risk of contacts developing disease by 50–60% in 2 years [7]. Development of a leprosy-specific vaccine that boosts T-cell immunity for many years is an objective being sought.

Gambian sleeping sickness is caused by human African trypanosomiasis (transmitted by the Tsetse fly) is localized to Western and Central Africa. African sleeping sickness epidemics in the twentieth century resulted in the loss of millions of lives, but the disease is now rare and is targeted for elimination by the WHO [8]. Key elimination strategies include active screening for disease, Tsetse fly control, targeting high-risk groups, and increased access to diagnostic tests [6]. *T. brucei gambiense*

causes the more chronic Gambiense sleeping sickness in Western and Central Africa with humans as the main reservoir, whereas the more acute rapidly progressive disease caused by *T. brucei rhodesiense is* found in eastern and southern Africa, where the main reservoir is in domestic and wild animals [8]. Thus, active screening and treatment of asymptomatic *T. brucei* gambiense may help control and eliminate the disease.

Visceral leishmaniasis (Kala-azar) in the Indian subcontinent, caused by a parasite (*Leishmania donovani*) transmitted by sandflies, mainly in the poorest communities, the rate has been falling with control measures. The strategy for elimination consists of rapid case detection, treatment of cases, and vector control using indoor residual spraying [9]. Sustained elimination may require a better understanding of the transmission dynamics, improved diagnostics, and treatment of the post-Kala-azar dermal leishmaniasis (PKDL) [6, 9].

Chagas disease, caused by *Trypanosoma cruzi,* is mainly transmitted by the redovid (kissing) bug in poor, rural communities of Latin America and less by congenital and blood transfusion transmission. Infection is usually contracted in childhood and often remains undiagnosed until many years later, when some patients present with cardiac or gastrointestinal manifestations. The current strategy for control of the disease is indoor residual spraying for the vector, but active transmissions still occur in several regions [10]. Dynamic transmission modeling, indicate that highly effective vector control combined with screening diagnostic tests and trypanocidal treatment in infected cases would greatly reduce transmission, incidence of infection, and prevalence [11].

9.3 Mass Drug Treatment/Administration Background

Mass drug treatment or administration (MDA) is the cornerstone program for control or elimination of the five to seven most prevalent NTDs by the WHO. It is based on the principles of preventive chemotherapy by delivering inexpensive essential antimicrobials, where populations or communities are offered treatment to prevent disease without individual diagnosis [12]. The concept of MDA for infectious disease in neglected populations is not new and was first applied outside the tropics. In the deep south of the USA, soil-transmitted helminths, particularly hookworm, was very prevalent in school-age children (40%) in the early twentieth century. In 1910, the Rockefeller Sanitary Commission sponsored an eradication campaign, combining MDA with anthelmintics, sanitation, and education with great success [13]. This resulted in long-term improvement in health, education, and economic development of the poorest in the USA. However, the use of MDA for NTDs as preventive chemotherapy was first pioneered in China [14].

China used to be one of the most heavily burdened countries in the world with lymphatic filariasis (LF), with at-risk population of 330 million in the 1970–1980s and microfilaria rates in endemic areas varying from <5% to >30% [15]. MDA with diethylcarbamazine (DEC) was first initiated in 1972 to two hyperendemic areas

and later expanded to other endemic areas with the aim to reduce microfilaremia rate to <1%. Three schemes with DEC for LF control in China were instituted: repeated blood surveys and treatment, treatment of microfilaremia cases and mass chemotherapy of the whole population in endemic areas, and treatment of cases with DEC fortified salt [15]. The 0.3% DEC salt was well tolerated with rare mild side effects and was given intermittently in two to four courses (3-month treatment) with the total dosage of 9–13.5 g/person. Intensive surveillance over 10 years found transmission was interrupted with no new LF case in China [16] and in 2007 the WHO confirmed that China had eliminated LF as a public health problem [15].

Currently, more than 700 million people have received MDA annually for NTDs in the past 20 years and 1.9 billion people need to receive MDA annually over several years to achieve the WHO target [12]. The five NTDs controlled primarily by MDA include: (1) soil-transmitted helminthiasis, (2) lymphatic filariasis (LF), (3) onchocerciasis, (4) schistosomiasis, and (5) trachoma. Although controversial and not included in the WHO NTDs for MDA, several studies have assessed the effect of MDA for malaria control in low endemic areas.

9.4 Soil Transmitted Helminthiasis and Mass Drug Treatment

Intestinal nematode parasites, roundworm (*Ascaris lumbricoides*), hookworms (*Ancylostoma duodenale* and *Necator americanus*), and the whipworm (*Trichuris trichiura*) are estimated to infect 1.5 billion people globally [17], but in fact, only a minority have symptoms or experience any morbidity. *Ascaris* and *Trichuris* are most commonly found in school-aged children, resulting from ingestion of food, water, or soil with parasitic eggs from the feces of infected individuals; and hookworm highest burden are typically found in adults, resulting from larvae of contaminated soil penetrating barefooted persons [18]. Thus, they are infections of the socially and economically deprived of poor sanitation habitats. These three parasites often coexist together in children in poor developing countries with malnutrition, growth stunting, intellectual retardation, cognitive and educational impairment [19], which stimulated the WHO target for elimination. However, the cause and effect of the helminthic infestations and morbidity are controversial and the results of MDA and outcome have been mixed.

The vast majority of infected children or adults are asymptomatic but moderate to heavy infections can cause symptoms. Heavy burden of *Ascaris* worms most commonly produce abdominal distension and discomfort, but rare complications in young children include partial small bowel obstruction, intussusception, volvulus, appendicitis, pancreatic and biliary obstruction with secondary cholangitis [19]. Trichiura (whipworm) mainly resides in the cecum and heavy infections can result in chronic dysentery and rectal prolapse in children and may be associated with anemia [19]. Hookworm heavy infestation can result in iron deficiency anemia and

fatigue that can be of concern in pregnancy with a possible adverse effect on the fetus, and extremely rare is the association with hypoproteinemia and anasarca [19]. It is estimated that 40 adult worms in the small intestine are sufficient to reduce hemoglobin below normal.

WHO guidelines for MDA to eliminate soil-transmitted helminths in endemic regions with prevalence ≥20% to <50% is single-dose albendazole or mebendazole to school-aged children (75% coverage) yearly for 5–6 years, and two to three times a year with prevalence ≥50% with the aim of lowering the prevalence <1% [18]. To date, many developing countries have implemented MDA for soil-transmitted helminths in targeted high endemic areas for several years. The efficacy of these MDA programs can be assessed in two ways: (1) random stool surveillance of students in treated areas to assess prevalence of these parasites after several years of treatment or MDA; (2) posttreatment assessment of clinical morbidity compared to pre-MDA, such as the prevalence of anemia, cognitive impairment, and school performance.

A few studies have recently been published on the effect of MDA on the prevalence of helminthic infections in different countries of the world. The government of Bangladesh had implemented biannual MDA with mebendazole (500 mg) to school children since 2008 and after 8 years several studies found a high prevalence of helminthic infections in many areas of the country [20]. Major barriers associated with the MDA program included were drug distribution policy, accessibility to schools, poor record keeping, follow-up, and information dissemination. In a study from southern Ethiopia, 3 years after the initiation of MDA, a community-based assessment on the burden of intestinal helminths by microscopic stool examination from primary school-aged children was performed [21]. Intestinal helminths were found in 46.3% of participants with 6.1% dual infections, and risk factors for infection were a failure to wash fruits and vegetables and habit of swimming. Thus, the investigators conclude that MDA for soil-transmitted helminths (STH) should be integrated with deworming, water, hygiene, and sanitation practices and health education [21]. It should be noted that successful control of STH with MDA has only been associated with economic development and hygiene improvement, as shown in South Korea [22].

What is the evidence that MDA for helminths improved morbidity of endemic communities in developing countries? Models suggest that MDA with mebendazole every 6 months with 80% coverage for 5–6 years in Vietnam could substantially reduce intestinal helminths prevalence and reduce morbidity by 67.7% [23]. Two recent reviews of the clinical benefit of MDA chemotherapy for helminths have been published. In a Cochrane systematic review of 45 trials, the authors concluded that MDA of all children in endemic areas show significant evidence that this does not improve nutritional status, hemoglobin, cognition, school performance, or survival [24]. In a more recent review on the benefits of large-scale deworming programs, it was concluded that there is a paucity of evidence of improvement in direct morbidity measures such as changes in height, weight, hemoglobin, and cognition [25].

9.4.1 Concerns of Mass Chemotherapy for Helminthiasis

There are two major concerns with MDA for STH in endemic regions: (1) development of widespread drug resistance in helminth species, and (2) increased risk of allergic diseases in the treated populations. Mass chemoprophylaxis has been used in dairy animals and widespread anthelmintic resistance has been observed in helminths infecting small ruminants and cattle [26, 27]. There is a paucity of studies in humans to assess drug resistance to anthelmintic drugs (benzimidazoles). Beta-tubulin gene mutations or single nucleotide polymorphisms (SNPs) have been linked to benzimidazole resistance in several nematodes in animals [28]. One study in Brazil has assessed for the presence of SNPs in nematodes recovered from children of six states where MDA has been used for STH. In 62 stool samples no mutations were found in *A. lumbricoides* eggs, but in 48 patients mutations were found in 1.1–1.4% of *N. americanus* eggs [29]. Thus, in the early years after MDA benzimidazole resistance has not emerged as a problem as yet, but there is a potential for increased drug resistance in hookworms. Assessing the clinical response to single-dose treatment in patients with intestinal nematodes, where MDA has been used can also determine the development of drug resistance. In a recent study, single-dose albendazole 400 mg was found to be highly effective against *Ascaris* spp. (cure rate 91.4%), less effective for hookworm (cure rate 58.3%) but intensity reduction was still adequate, 88.9% [30]. Thus, failing to detect clinical resistance in STH to date.

In regions of the world where helminth infections are high, the burden of allergic/atopic diseases is low and it is postulated that parasitic infections may protect against allergic disorders. Two recent studies have addressed this issue. In an open, cluster-randomized trial in Uganda 26 high-schistosomiasis-transmission villages were randomized to standard (annual praziquantel plus 6-monthly single-dose albendazole) MDA or intensive community-wide (quarterly single-dose praziquantel plus albendazole daily for 3 days) MDA [31]. There was no difference in atopy, allergy-related diseases, or helminth-related pathology after 3 years. However, this study did not include a group without anthelmintic therapy and, thus, did not address the issue fully. In a study from Indonesia, the prevalence of skin reactivity to allergens was evaluated before and 1 year after albendazole treatment in 150 school children [32]. The prevalence of STH decreased from 19.6% before to 6% after treatment and allergic skin test reactivity increased from 18.7% to 32.7%. Although larger prospective or placebo-controlled trials are needed to confirm these findings, the data suggest that MDA of STH can increase atopic/allergic diseases.

9.5 Mass Drug Treatment of Lymphatic Filariasis

Lymphatic filariasis (LF), caused by the mosquito-borne nematodes *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*, is endemic in 73 countries with 68 million people infected and 20 million suffering from chronic morbidity [33]. The

clinical manifestations include subclinical lymphatic damage in children, then most commonly hydrocele, chronic lymphedema of arms and legs (elephantiasis) in adults, and associated mental health disorder, marginalization, social stigma, and economic hardship. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was set up in 2000, with the aim to eliminate LF worldwide as a public health problem by 2020 [33]. WHO programs implemented to interrupt transmission include at least five rounds of annual MDA to >65% of the endemic population with two-drug combination: (1) DEC plus albendazole (DA); (2) ivermectin plus albendazole (IA) in areas co-endemic for onchocerciasis; and (3) albendazole twice yearly in areas co-endemic for loiasis [34]. Since 2000, a total of 6.7 billion treatments have been given to >850 million people at least once and in 2016 the total population requiring MDA was decreased by 57.9% from 1.2 billion people in 2000 to 495.6 million persons in 40 countries [34]. In the same period, the burden of disease in disability-adjusted life years declined from 1.9 million to 1.2 million (36.8% reduction) [17]. After 13 years of MDA for LF, the greatest reduction in prevalence is for microfilaremia (68%), followed by hydrocele (49%) and lymphedema (25%) and chronic disease has been averted in 79.20 million people [35].

However, recent modeling suggests that annual MDA strategies will be insufficient to achieve elimination of LF by 2020, and biannual triple-drug therapy [ivermectin, DEC, and albendazole (IDA)], holds the best promise of achieving this target [36]. Recent studies from different countries have reported focal hotspots or persistent low-level LF transmission after several years (6–16 years) of MDA, which suggests that resurgence of LF is likely to occur after discontinuation of the MDA programs [37–39]. In Myanmar for instance, after six rounds of annual MDA persistence of filarial infection and transmission continue with the prevalence of antigenemia in 2.63% and microfilaremia of 1.03% [39]. Most recently, a small randomized trial in Papua New Guinea compared the effectiveness of a single dose of three drugs (IDA) compared to annual two-drugs (IA) for 3 years for sustained clearance of microfilaremia [40]. The 3-drug regimen cleared microfilaremia in 55 of 57 patients (96%) at 36 months compared to 43 of 52 (83%) participants given a single 2-drug regimen ($p = 0.02$), but was equivalent to the annual 2-drug regimen for 3 years with clearance in 51 of 52 (98%) participants at 36 months.

9.5.1 Viewpoint of Elimination of Filariasis

There is no doubt that MDA has resulted in a marked reduction of the global burden of LF, but achieving the goal of worldwide elimination as a public health problem by 2020, in 1 year, is clearly unattainable. Triple-drug regimen (IDA) appears to be very promising but may not be needed biannually or annually as indicated by some models, based on the recent trial it could be given every 3 years for two to three cycles. However, this should be combined with improved vector control, education to enhance greater participation of communities with >80% uptake of treatment and improved drug delivery to participants. Assessment of response should be performed

during the program but most importantly several years after cessation of MDA. Studies should incorporate molecular methods to assess for drug-resistant mutations.

9.6 Mass Drug Treatment of Onchocerciasis

Onchocerciasis (called river blindness) is caused by the filarial nematode *Onchocerca volvulus* that is transmitted by the Simulian blackflies, endemic in 31 African countries and localized foci in Brazil and Venezuela [41]. The adult worms live in subcutaneous nodules and produce thousands of microfilariae which preferentially reside in the skin and the eyes, and produce inflammatory reaction on dying to produce symptoms and disease. Chronic cutaneous onchocerciasis (onchodermatitis) produces severe pruritus with hyperpigmentation or patchy depigmentation, scarring, and lichenification (called leopard skin), but eye involvement may result in sclerosing keratitis, iridocyclitis, retinitis, optic neuritis, and blindness [41]. Worldwide onchocerciasis is considered the second leading infectious cause of blindness. The number of people still living with onchocerciasis is estimated at 15–18 million, 99% residing in Africa, and 750,000 with reduced vision or blindness [17, 41]. The adult worm may live for 15 years and contribute little to the pathology and the microfilariae live for 6–12 months and are continually replenished by fertile adult female nematodes or reinfection by blackfly bites.

Attempts to control river blindness were instituted since 1974, primarily with insecticides for vector control and nodulectomy/anthelmintics for infected cases. Although, humans are the only reservoir eradication of the vectors was difficult because of the remote rural locations along rapid moving rivers. DEC was tried but due to its rapid microfilaricidal action, severe side effects occurred from the dying larvae with worsening vision and skin reaction [42]. Ivermectin has a slower microfilaricidal action and similar paradoxical reactions are not usually seen. There is presently no macrofilaricidal drug to eradicate the adult worms. Since 1987, ivermectin has been donated by Merck through the Mecitizan Donation Program and nearly 132 million people have received treatment and currently, 198 million people live in endemic areas, but 1.4 million people no longer require treatment [43]. The current strategy for control/elimination in endemic regions includes MDA with ivermectin annually or semiannually with >80% coverage, typically for 12–15 years and supplemental vector control in three countries (Equatorial Guinea, Uganda, and Tanzania) [41]. In regions of central Africa where coinfection with *Loa loa* occurs ivermectin is avoided because of severe reactions such as encephalopathy and death.

MDA with ivermectin since the 1990s has been highly successful in the Americas, where transmission has been eliminated or interrupted in 11 of 13 original foci of onchocerciasis with two of six countries in South America remain endemic [41]. Four countries in the Americas (Columbia, Mexico, Ecuador, and Guatemala) have completed the WHO verification process for elimination [44]. In Africa, morbidity and transmission have been reduced but not eliminated, but great success was

achieved in the savanna areas of 11 countries by vector control and ivermectin treatment before the closure of the Onchocerciasis Control Programme of West Africa in 2002. It is estimated that 600,000 cases of blindness were prevented by 2002 [41]. Progress in the control of onchocerciasis continue in Africa with the first confirmed elimination focus in Abu Hamed, Sudan in 2016 [45] and three countries (Ethiopia, Nigeria, and Uganda) had stopped MDA in at least one subnational area and started the posttreatment surveillance [46].

9.6.1 Concerns with MDA and Control of Onchocerciasis

There are many challenges in Africa remaining to achieve the elimination of onchocerciasis as a public health problem even by 2030. It is now evident that to achieve this goal will need coverage of the total population (240 million) at risk with MDA, which is now at 69.6% [46]. Moreover, targeting hyperendemic areas with onchocercal nodules >20% and >1% blindness for MDA appears too limited, as in hypoendemic areas without nodules on examination could still have microfilaremia prevalence of 20% [43]. The WHO is now taking steps by scaling up the mapping of areas for elimination so that no onchocerciasis—endemic district is excluded for MDA. Logistic problems still exist in some endemic countries of Africa, besides failure of full participation, and these include ongoing strife and civil disturbance (i.e., Yemen), noncompliance of participants, and delivering drugs to remote geographical locations [42]. For instance, after 15 years of MDA with ivermectin there is still evidence of continued transmission in *O. volvulus* in the west region of Cameroon [47], probably from multiple reasons. One possible explanation is the suboptimal response due to resistant mutations of the microfilariae. This issue has been raised before after suboptimal response to ivermectin was observed in Ghana, where adult worms were resuming microfilaria reproduction more rapidly after ivermectin than normally expected [47]. Investigation for resistant mutations to ivermectin should be included in the WHO elimination program for onchocerciasis. In some African countries, poor mobilization, medicine distribution, and program penetration have led to low coverage and persistent transmission [48].

9.6.2 Future Directions for Elimination of Onchocerciasis

Some recommendations and models have suggested that ramping up MDA with ivermectin biannually or quarterly with vector control would accelerate the elimination of the process [49]. Besides the use of insecticides, community-directed vector control may be best achieved with “slash and clear” interventions to clear the breeding sites of the vegetation that represent the primary blackfly larvae attachment point [50]. Consideration should also be given for annual use of a structurally similar drug as ivermectin (half-life <1 day), moxidectin with half-life of 20–43 days, as

a single dose of the new drug is more effective than single dose of ivermectin, and would have a greater impact on transmission intensity and the effect would be less dependent on dosing relative to peak transmission season as that of ivermectin [51, 52]. Combining ivermectin with doxycycline (100–200 mg/day for 6 weeks) is more effective than either drug alone, but it is not suitable for MDA. Doxycycline targets the endosymbiotic Wolbachia species and interrupts microfilarial embryogenesis, decreasing, or eliminating microfilaria for >18 months after treatment [53]. It also has a modest effect on the adult worms, reducing the numbers by 50–60% [54]. However, it would be worthwhile using doxycycline for the treatment of patients with onchocerciasis along with MDA for the community population in endemic areas, as this may help interrupt transmission.

9.7 Mass Drug Treatment of Schistosomiasis

Schistosomiasis (known as bilharziasis) is a chronic parasitic disease caused by blood flukes (trematodes) that are transmitted by infected water, during routine agriculture, domestic, occupational, and recreational activities via the intermediate hosts, freshwater snails. Lack of hygiene and certain habits such as swimming, wading, or fishing in infested water put vulnerable people especially school-aged children at risk. Estimates in 2016 show that at least 206.4 million people require preventive treatment and 78 countries (42 in Africa, 16 in eastern Mediterranean, 10 in the Americas, six in the western Pacific, three in Southeast Asia, and one in Europe) have schistosomiasis transmission [55]. Schistosomiasis causes a wide range of symptoms and chronic debility, depending on the species and worm burden and is considered the third most frequent, debilitating parasitic infection in the tropics after malaria and intestinal helminthiasis.

There are five human species of *Schistosoma*, but the three major species responsible for most human affliction are *Schistosoma mansoni* (reside in mesenteric venules of the colon) endemic in Africa, South America, and the Caribbean; *Schistosoma haematobium* (reside in vesical venous plexus) endemic in Africa, the Middle East, India, and Turkey; and *Schistosoma japonicum* (reside in mesenteric venules of the small intestine) endemic in Asia only (China, Indonesia, the Philippines, and Thailand) [56]. The other minor human species are *Schistosoma intercalatum*, found in central and West Africa rain forest, and *Schistosoma mekongi*, which is found in the Mekong river basin of Southeast Asia. It is estimated that schistosomiasis causes 15,000 lives lost annually and 1.75–2.0 million disability-adjusted life years lost, of which 85% are in sub-Saharan Africa [17].

The control of schistosomiasis is based on MDA of at-risk populations in endemic countries, access to safe water, improved sanitation, hygiene education, and snail control [55]. Preventive chemotherapy with praziquantel MDA for at-risk populations has been the main strategy for the control of schistosomiasis by the WHO since 2001. The strategy was for the community- or school-based treatment program depending on the prevalence of infection. The most vulnerable and likely

to be infected are school-aged children (SAC; 5–14 years old). In low-risk communities, the strategy is to treat all SAC every 3 years and treat suspected cases; in moderate-risk communities, the aim is to treat all SAC and at-risk adults every 2 years; and in high-risk communities, the approach is to treat all SAC and at-risk adults annually [57]. Praziquantel 40 mg/kg was to be used to treat a minimum of 75% and up to 100% of all SAC, but new guidelines set for 2020 were 100% geographic coverage, 75% national coverage and <5% prevalence of heavy infections [57]. In 2015, 61 million people received praziquantel MDA, out of the estimated 218 million people in 52 countries who require treatment [58].

How effective is the MDA of praziquantel in controlling schistosomiasis in endemic areas? In Togo annual, integrated, community-based MDA for schistosomiasis began in 2010 with programmatic coverage of over 94%, and after 4–5 years the prevalence of schistosomiasis has declined from 23.5% to 5.0% ($p = 0.001$) [59]. For disease elimination, the target is <1% prevalence which requires 75–100% coverage of SAC. However, the global coverage rate reported by WHO in 2016 was found to be 35.6% to 53.0% among SAC and 14.3% among adults [60]. This is exemplified by findings in the Philippines where the national coverage rate is 43.3% and noncompliance to MDA was common (about 27%) [61]. In Egypt, extended selective treatment with praziquantel in the Nile Delta was introduced in 1992 and upgraded to MDA in 1997, but the transmission of *S. mansoni* in high-risk areas in the Nile Delta remains uninterrupted with village prevalence rate of 16.5–49.5% [62]. Two recent studies from Kenya have reported a lack of reduction in Schistosome burden or prevalence of *S. mansoni* in SAC after 4–5 years of MDA [63, 64].

9.7.1 Viewpoints and Concerns with Elimination of Schistosomiasis

It does not appear that schistosomiasis can be eliminated as a public health concern even by 2030 unless new and more effective approaches are taken. Models have indicated that expanded MDA coverage to at least 85% of SAC and 40% for adults, and enhanced snail control and WASH (water, sanitation, and hygiene) measures for effective control or elimination are needed [65]. But these measures may be inadequate without proper education of the target communities. An issue that has not been fully addressed is the development of drug resistance to praziquantel by using genetic methods for surveillance after MDA. Resistance to praziquantel was first reported in *S. mansoni* in the mid-1990s [66] and a number of reports suggested reduced response to praziquantel MDA [67–71], but despite widespread use only limited resistance has been recorded [72–75]. It has been suggested that supplementing praziquantel with new antischistosomal drugs or repurposing developed drugs with these properties (e.g., miltefosine, mefloquine, and moxidectin) targeting different parasite development would be more effective in controlling/eliminating schistosomiasis and would reduce the risk of drug resistance [76].

9.8 Mass Drug Treatment of Trachoma

Trachoma is the commonest infectious cause of blindness worldwide, due to recurrent chronic infection of the eyes with *Chlamydia trachomatis* serovars A, B, Ba, and C [77]. Chronic keratoconjunctivitis leads to corneal opacification and blindness. Poor sanitation, lack of facial washing, crowded living conditions, lack of clean water and toilet facilities, exposure to flies or contact with infected persons increase the spread of the infection. Since the institution of WHO programs to reduce active (follicular) trachoma in 1999, there has been a dramatic decline in trachoma burden. In 2009, it was estimated that 40 million people had active trachoma [78] and in 2016 the worldwide prevalence was estimated at 3.3 million [17]. Elimination has been successfully achieved in several countries recently, Morocco, Laos, Nepal, and Mexico [80]. However, trachoma was previously endemic in North America and Europe but was eradicated with improved sanitation and socioeconomic conditions. Mass distribution of azithromycin (single observed oral dose at 20 mg/kg) annually for 3–5 years to children 1–9 years is the mainstay of the WHO program to control trachoma in communities with >10% prevalence, aim to achieve <5% prevalence, with ≥80% coverage of the targeted population [81]. This is a key component of the SAFE (surgery for trichiasis, antibiotics, facial cleanliness, and environmental improvement) strategy.

Despite the excellent progress in the fight against trachoma, hyperendemic areas still exist in Ethiopia with some severely affected districts treated for 10 years [80] and 158 million people live in 37 endemic countries (WHO, Trachoma; Key facts, October 2018). In 2017, 83.5 million people received MDA for trachoma which is only 52% of the global targeted coverage and short of the 80% target. Trachoma is now estimated to be responsible for the blindness or visual impairment in 1.9 million people [79]. In a recent study of hyperendemic trachoma in northern Ethiopia, discontinuation of mass azithromycin after 4 years of treatment was associated with reappearance after 3 years and in some communities, 7 years of continuous treatment did not eliminate the infection [82]. Although transmission models had suggested that biannual MDA may be more effective in hyperendemic areas, 3 clinical trials showed no significant differences in recurrence after 3–4 years of treatment [83]. The best strategy for elimination in areas of hyperendemicity of trachoma is uncertain, but elimination is not likely to be achieved globally by 2020 and doubtfully even for 2030. A combination of increased coverage approaching 100% in endemic areas, MDA, facial hygiene, and improved sanitation appears to be the best option.

9.8.1 Concerns with Mass Drug Treatment of Trachoma

More than 700 million doses of azithromycin have used in trachoma endemic regions as part of the trachoma-control program [84] and this raises serious questions on the effect of fueling bacterial macrolide drug resistance. Development of macrolide resistance by *C. trachomatis* has not been shown to be a problem or concern [85], however, the development of resistant mutations by other bacteria colonizing treated patients has been reported. In a recent systematic review of antimicrobial resistance following MDA of azithromycin, 19 studies were used for analysis, 12 assessed *Streptococcus pneumoniae* and 8 other bacteria [86]. Macrolide resistance after MDA was reported in three of five organisms studied, but the review confirmed lack of resistance in *C. trachomatis*. Overall, the studies showed an increase in macrolide resistance in *S. pneumoniae* soon after treatment, which revert to baseline over time. Five studies included untreated control group and found marked increase resistance in *S. pneumoniae* in communities treated with azithromycin but not in untreated districts. Increased frequency of MDA (biannually) increased the selection of macrolide resistance. Worsening macrolide resistance was also found with *Staphylococcus aureus* and *Escherichia coli* after MDA, but these bacteria are not usually treated with macrolides. The reviewers noted absence of studies assessing macrolide resistance in bacteria where azithromycin is commonly used such as *Neisseria gonorrhoeae, Salmonella typhi, Shigella* spp., and *Campylobacter* spp. [86]. Emergence of resistance in *Treponema pallidum* after mass azithromycin programs for yaws has been reported [87], but not assessed in the studies reviewed.

9.8.2 Viewpoint on MDA for Trachoma

MDA of azithromycin benefits appear to outweigh the potential downside of increased macrolide *S. pneumonia* resistance which is a transitory effect, and macrolides are not usually used to treat pneumococcal infections especially in trachoma endemic countries. Furthermore, there is increasing evidence that MDA of azithromycin reduces the all-cause mortality by 14.4% in children <5 years of age by unclear mechanism(s) [88].

9.9 Mass Drug Treatment of Malaria

Malaria is not an NTD but in the past decade, there has been renewed interest in MDA for malaria control. It is estimated that malaria affects ≈210 million people globally resulting in 0.5 million deaths annually, with ≈90% malaria deaths in Africa [89]. MDA was initially implemented in the mid-twentieth century for

control of malaria, but it was abandoned for multiple reasons including questions of efficacy, feasibility, and encouraging drug resistance [90]. In 2015, the WHO recommended MDA for malaria in the following settings [91]: (1) use of MDA to interrupt transmission of falciparum malaria in endemic island and in low-endemic non-island settings approaching elimination with minimal risk of reintroduction, where there is good access to treatment, and implementation of vector control and surveillance; (2) as a component of accelerated malaria elimination in areas of the Greater Mekong Subregion with the threat of multidrug resistance, with good access to treatment, vector control, and surveillance; (3) as part of an immediate response to an epidemic to rapidly reduce morbidity and mortality, while other interventions are put in place; and (4) complex emergencies during exceptional circumstances, where the health system is overwhelmed and unable to serve the communities.

Investigators using consensus modeling reported on the effect of MDA for malaria and concluded that it would potentially reduce transmission for a limited time, but is not an effective replacement of existing vector control [92]. Unless elimination is achieved, MDA has to be repeated regularly for sustained effect and the major concern is encouraging the proliferation of multidrug resistant *Plasmodium falciparum*. It is too early at this time to determine the effectiveness of MDA for malaria, but a few studies have been reported to date with mixed results. In a preliminary report of mass chemoprevention for malaria conducted in 2012, residents of three remote villages, with submicroscopic asymptomatic malaria present in 55–68%, on the Thai–Myanmar border were treated with one to three doses of dihydroartemisinin-piperaquine (DAP) [93]. *P. falciparum* was eliminated during the 6-month follow-up period (prevalence fell from 7% to 0%); and *P. vivax* persisted (prevalence fell from 85% to 35%), but primaquine was not used. Of note is that 62% of those with *P. falciparum* carried single point mutations in the PF kelch protein marker of artemisinin resistance. A more recent observational study in this region, four townships of eastern Myanmar malarial hotspots (>40% malaria with 20% *P. falciparum*) received targeted MDA with DAP plus single-dose primaquine (PMQ) monthly for 3 months in addition to malaria post (increased access to early diagnosis and treatment of clinical malaria). The incidence of *P. falciparum* malaria decreased by 98% in the townships and MDA was associated with a fivefold decrease incidence within the hotspot villages [94]. Interestingly, the wild-type genotype for K13 molecular markers of artemisinin resistance was stable over the 3 years (39%). Similar positive results were reported after three rounds of DAP in Cambodian villages in a controlled randomized trial with *P. falciparum* incidence significantly lower in treated villages 12 month post-intervention compared to untreated villages with absence of clinical cases for a year, and decrease in vivax malaria by half [95]. Preliminary results from a trial in Laos also showed an 85% reduction in asymptomatic *P. falciparum* after three rounds of DAP/PMQ [96].

In a study from a highly endemic region of Africa (Anjouan Island, Union of Comoros), large-scale artemisinin-piperaquine (AP) with or without PMQ resulted in a dramatic reduction of malaria cases [97]. The study involved two cohorts totaling 86–93% of the ≈322,000 inhabitants treated monthly for 3 months from October to December 2012. The monthly rates of malaria fell from 310.8 to 2.06 per

100,000 in the AP plus PMQ-treated villages and from 412.1 to 12.60 per 100,000 in the AP-treated villages; and the prevalence PFK13 propeller polymorphisms remain unchanged before and after MDA [97]. This is in contrast to the findings of a cluster randomized trial of two rounds (a month apart) of MDA with DAP plus PMQ in a low malaria-endemic setting (pre-elimination) in Zanzabar [98]. No difference in cumulative malaria case incidence was found between the control and intervention groups 6 months post-MDA (4.2 and 3.9 per 1000 population); nor difference in PCR-determined parasite prevalence 3-months post-MDA (1.4% and 1.7%). The intervention coverage was high, over 87–91% with adherence of 82–93%, and travel outside Zanzabar was similar between the groups [98]. It is possible that the failure of MDA in Zanzabar was due to too few numbers of MDA and further trials with more total MDA are warranted.

9.9.1 Concerns of MDA for Malaria

The major concern of MDA for malaria is the risk of increasing multidrug resistance which to date has not been found in these early reports. The MDA of the regimens appears to be safe and well tolerated.

Historically there is a precedent for MDA for malaria elimination with success. In the past, primaquine mass administration was used extensively to eliminate *P. vivax* from temperate regions [99]. Malaria was also eliminated from a small island in the Southwest Pacific, where the entire population of 718 inhabitants was treated with 9 weekly doses of chloroquine, pyrimethamine/sulfadoxine, and PMQ in 1991 [100]. White has argued somewhat convincingly that MDA for malaria, if the targeted populations are chosen appropriately with coverage of >80%–100%, should not result in the proliferation of drug resistance but may decrease the risk [101]. In the laboratory, the rate of spontaneous mutation from drug-sensitive to resistant alleles was found to be 10^{-8} per replication, and a greater number of parasites present in the body increases the chance of selecting drug-resistant mutants which keep increasing due to their selective advantage [102]. In malaria-endemic areas, many more people have an asymptomatic infection with low parasitemia than symptomatic malaria with >1000-fold greater parasite burden. Thus, symptomatic patients with high parasite burden are the main source of resistance emergence, especially when treated with low dose or inadequate antimalarial drugs [103]. MDA of targeted communities aim is to eradicate parasitemia from asymptomatic subjects and to prevent symptomatic malaria and its transmission, and can reduce the emergence and spread of resistant malaria in the population [101]. However, the problem of malaria drug resistance is more complex and involves the parasite genetic diversity, host, and vector factors, baseline level of drug resistance in the communities, and drug combination used for the MDA.

Emerging artemisinin resistance along the Thailand–Cambodia border in the past 10 years has resulted in increasing rates of failure to artemisinin combination therapy, such as artesunate-mefloquine and artemether-lumefantrine resulting in

DAP being used as the drug of choice in Cambodia and for MDA in field trials [104]. Artemisinin resistance appears to be a complex mechanism that may result in low-level resistance that may allow the elimination of the mutated parasite even with the *kelch 13* mutations, in the absence of the partner drug resistance the infection can be cleared with adequate treatment [104]. However, in several regions of Cambodia increased artemisinin-resistant mutations and emergence of piperaquine resistance have resulted in DAP treatment failure of up to 46% in northern and western Cambodia [105, 106].

Overall, attempts to eliminate malaria in localized, low transmission areas (with the community full participation and governments support), combined with vector control (permethrin-treated clothing, indoor residual insecticide, etc.), and MDA with DAP plus PMQ may be worthwhile. However, it is very important to educate members of the community and to elicit >80% participation of the inhabitants as anything less will likely lead to eventual resurgence of multidrug-resistant malaria. For instance, in a pilot trial in villages of Eastern Myanmar three rounds of MDA were associated with reduction of malaria prevalence at 3 months post-intervention, but not at 9 months which could be attributed to low participation; 57–61% coverage in small villages and only 28–29% in larger villages [107]. Adding single low-dose PMQ is desirable to reduce transmission of the *P. falciparum* gametocyte and may prevent the propagation of any acquired drug resistance. Combination with ivermectin may be useful as it has been shown to kill wild *Anopheles* and suppress malaria transmission in West Africa and inhibit sporogony in *P. vivax* [108]. A study is underway in Southeast Asia to assess the effect and safety of ivermectin in combination with DAP/PMQ [104]. Table 9.2 summarizes MDA for NTDs and malaria.

Table 9.2 Neglected tropical diseases and malaria treated with MDA

Diseases	Status	MDA control	Comments
Helminthiasis (ascariasis, trichuriasis, hookworm)	> 1 billion globally	ABZ or mebendazole 1–3 annually for 5–6 years	No morbidity benefit. Elimination unlikely, 10% heavy burden
Lymphatic filariasis	68 million in 73 countries mainly Africa, SE. Asia	IVM/ABZ (Africa), DEC/ABZ (elsewhere)/year × 6	Decrease morbidity, elimination possible
Onchocerciasis	15–18 million, 99% in Africa	IVM 1–2 annually for 12–15 years	Improved morbidity, elimination possible
Schistosomiasis	240 million in 54 countries	PZQ every 1–3 years for 5–6 years or more	No morbidity benefit. Elimination unlikely
Trachoma	3.3 million in 37 countries	Annual azithromycin for 3–5 years	Marked benefit, can be eliminated
Malaria (*P. falciparum*)	219 million in 90 countries, 92% of cases and 90% deaths in Africa	DAP + PMQ monthly for 3 or more months	Targeted areas, GMS promising results

Abbreviations: ABZ albendazole, IVM ivermectin, DEC diethylcarbamazine, DAP dihydroartemisinin-piperaquine, GMS Greater Mekong Subregion, PMQ primaquine, PZQ praziquantel

9.10 Unintended Benefits of Mass Preventive Chemotherapy

There have been unintended benefits of mass preventive chemotherapy that have accumulated over the years (see Table 9.3), which were recently outlined by Hortez et al. [109]. Ivermectin in a single dose of 200 μg/kg used to control lymphatic filariasis or onchocerciasis reduced the prevalence of strongyloidiasis in Australian aboriginals and in Cambodia. It also reduced the rate of loiasis where *Loa loa* coexist with onchocerciasis and mansonellosis in the Amazon [109]. Large-scale studies in Africa and the South Pacific MDA of ivermectin demonstrated reduced burden of scabies and secondary impetigo [110]. MDA of azithromycin for trachoma has been shown to reduce the prevalence of yaws in New Guinea and Ghana [111], but there is a concern of increased macrolide resistance [87]. The unexplained benefit of MDA of azithromycin on infant mortality has been confirmed in a large, randomized follow-up study in Africa, which confirmed the lower mortality of preschool children who received azithromycin; the effect occurred primarily in the first 3 months of distribution of the drug [112].

There is also evidence that MDA of albendazole for intestinal parasites appears to have reduced the prevalence of oesophagostomiasis (caused by *Oesophagostomum bifurcum*) in northern Ghana and Tongo [109]. In addition, MDA of single-dose praziquantel for schistosomiasis may be beneficial in reducing the burden of opisthorchiasis in Southeast Asia and tapeworm infections [109].

9.11 Conclusion

MDA has had significant beneficial effects on the control and the path to elimination for lymphatic filariasis, onchocerciasis, and trachoma and appears promising for malaria control in specific areas and circumstances. It may not be very effective for the control of schistosomiasis and even less for soil-transmitted helminths, but there are unintended benefits of mass preventive chemotherapy. Studies need to continue to monitor for the development of drug resistance which so far has not been a major problem.

Table 9.3 Collateral benefits of mass preventive chemotherapy in tropical diseases

Drug	Collateral benefit	Targets
Albendazole	Oesophagostomiasis Strongyloidiasis	Helminths
Azithromycin	Child mortality Yaws	Trachoma
Ivermectin	Malaria transmission, loiasis, mansonelliasis, scabies, strongyloidiasis	Filariasis, onchocerciasis
Praziquantel	Trematodiases, taeniasis	Schistosomiasis

The most recent review of data from the Schistosomiasis Control Initiative, supported mutiyear, cross-sectional treatment programs in eight countries in subSaharan Africa with praziquantel MDA to control S. *mansoni* and S. *hematobium* [113]. Although the WHO program seems to be quite effective in the short term, it is unlikely to be sustainable in the long term. Praziquantel is only effective for adult schistosmes, but does not kill developing schistosmes to prevent reinfection [114]. Hence reinfection will likely develop soon after the treatment program is terminated.

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Chapter 10
Issues in Therapeutics of Some Bacterial Infections: Vancomycin Use, Osteomyelitis, Endocarditis, and *Staphylococcus aureus* Bacteremia

10.1 Vancomycin Therapeutics

10.1.1 Introduction

Vancomycin, a tricyclic glycopeptide which inhibit bacterial cell wall synthesis, was first approved for use by the United States [US] Food and Drug Administration [FDA] in 1958 and despite nearly 60 years of use its therapeutics is still mired in controversy [1]. It is considered the drug of choice for methicillin-resistant staphylococci, *Staphylococcus aureus* [MRSA] or *Staphylococcus epidermidis* [MRSE] or coagulase-negative staphylococci serious infections. Vancomycin is active against most Gram-positive aerobic cocci and bacilli except for intrinsic resistance by *Lactobacillus, Leuconostoc, Erysipelothrix, and Pediococcus* [1]. It is considered bactericidal for susceptible Gram-positive bacteria except it is bacteriostatic against enterococci, but it has slow bactericidal activity against *S. aureus* compared to β-lactam agents activity against methicillin-sensitive *S. aureus* [MSSA], resulting in worst clinical outcomes [2–4]. In a recent study of *S. aureus* bacteremia, the high failure rate of vancomycin [48%] in 119 patients was attributed to vancomycin tolerance [MBC/MIC ≥32] which was present in 26.7% of isolates [5].

10.1.2 Experience with Early Use of Vancomycin

The early use of vancomycin soon after its release was associated with high incidence of ototoxicity and nephrotoxicity which was later attributed in the 1970s to impurities in the early preparations [6]. Vancomycin became widely used in the 1980s with increased isolation of MRSA in hospitals. Ototoxicity was rarely reported and nephrotoxicity was infrequent [5%] and reversible and noted mainly in

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combination with aminoglycoside [7]. In vitro killing curve experiments with vancomycin against staphylococci did not demonstrate increased killing with stepwise increasing concentrations of 2–64 times the MIC [8]. Vancomycin has relatively slow bacterial killing and similar to other cell wall-active agents [β-lactams] exhibit primarily time-dependent killing with minimal relationship to concentration with maximal killing occurring at four times the MIC [9, 10]. In fact too high a concentration of the antibiotic above the MBC can result in a paradoxical effect of less bacterial inhibition [Eagle effect] seen with penicillin [11]. Recently the Eagle effect resistance has been described with vancomycin against *Clostridium difficile* at 64 times the MIC [12]. Consequently, there is no advantage of achieving high concentration of vancomycin above four times the MIC [8 μ/mL for MRSA] during the 24 h of daily treatment. The need to achieve higher concentration for higher bacterial load does not appear to be necessary, as in vitro data indicate that the MIC/MBC of vancomycin only increased one to twofold when the inoculum was increased from 5×10^5 to 5×10^7 [13].

10.1.3 Relationship of MIC and Efficacy of Vancomycin

An earlier study [2004] that may partly be responsible for current vancomycin therapeutics, reported that higher MICs [1–2.0 μg/mL] within the susceptible range was associated with vancomycin treatment failure in MRSA bacteremia [14]. Subsequently several individual studies found conflicting results. Three earlier meta-analyses on the topic suggested that elevated vancomycin MIC levels were associated with worst outcomes [15–17]. However, these studies mainly analyzed non-bacteremic infections of different sites in highly heterogeneous populations. A subsequent more robust study [systematic review and meta-analysis] was performed on the association between vancomycin MIC and mortality among patients with *S. aureus* bacteremia. This analysis included 38 studies with 8291 episodes of bacteremia treated with vancomycin with no difference in mortality in patients with high vancomycin MIC [≥1.5 mg/L] versus those with low MIC [<1.5 mg/L] [18]. The results were the same for studies that included only MRSA bacteremia [$n = 7232$]. Since this review in 2014, a recent report of a large cohort of invasive S. aureus infection [$n = 1027$] with 673 MRSA infections found high vancomycin MIC was not associated with increased 30-day mortality [19].

10.1.4 Pharmacodynamic and Dosing and Vancomycin

In 2009, the Infectious Diseases Society of America [IDSA] with collaboration of the American Society of Health-System Pharmacists [ASHP] and the Society of Infectious Diseases Pharmacists [SIDP] recommended vancomycin dosing of 15–20 mg/kg/dose every 8–12 h to achieve trough concentration between 15 and

20 mg/L for complicated MRSA infections including endocarditis, osteomyelitis, meningitis, and hospital acquired pneumonia, and >10 mg/L for other indications [20]. Previously, trough concentrations of 5–15 mg/L were considered appropriate, but due to the data on high vancomycin MIC and poorer outcome for MRSA infections, recommended trough concentrations were increased [21]. Targeting higher trough concentrations also was to increase the chance of achieving an area under the curve in 24 h [AUC_{24}]/MIC ratio ≥400, which was considered the best predictor of vancomycin efficacy in MRSA infection based on in vitro, animal models, and limited clinical studies [22]. However, even before these guidelines were published the clinical studies on AUC/MIC and high trough level and relationship to outcome were conflicting [23].

Another important question that should be addressed is: how accurate is the trough concentration of 15–20 mg/L with attainment of AUC/MIC ≥400? A recent retrospective analysis in 100 adult patients with MRSA infection has addressed this issue, and no difference in attainment of AUC/MIC ≥400 in patients with trough levels 10–14.9 mg/L was found when compared to those with trough vancomycin of 15–20 mg/L [24]. But higher trough level was associated with increased nephrotoxicity. This issue was also reviewed in pediatric patients recently. Eleven studies were included in the review and the authors concluded that in pediatric patients, vancomycin troughs of 6–10 mg/L are sufficient to achieve AUC/MIC ≥400 [25].

Moreover, these pharmacodynamics indexes have not been validated in MRSA endocarditis in animal models or humans. A recent study evaluated the relationship of the pharmacodynamics target [AUC/MIC ≥400] and vancomycin effect on sterilizing infected valves in MRSA experimental rabbit model. Three strains of MRSA [MICs 0.5–2.0 mg/L] were used in two groups of animals to compare the efficacy of vancomycin at standard doses to that of adjusted doses to achieve AUC/MIC ≥400 given for 48 h [26]. There was no significant difference in the sterilizing effect with the different dosing of vancomycin.

10.1.5 Clinical Studies on MRSA Infection with Vancomycin Pharmacodynamic Targets

Since the guidelines have been published in 2009, there have been multiple studies on vancomycin efficacy in severe MRSA infections and trough concentrations with conflicting results. Three systematic reviews and meta-analyses were published in 2015. One review included four prospective studies and 12 retrospective studies [n = 2003] and compared the impact of low [<15 mg/L] versus high [≥15 mg/L] vancomycin trough levels on efficacy [27]. There was no significant difference in treatment failure or all-cause mortality, but microbiological failure was higher in patients with low vancomycin trough levels. However, nephrotoxicity was significantly higher with vancomycin of ≥15 mg/L. In the second review, 17 studies [n = 2578] were included in the analysis comparing outcome with low and high

trough vancomycin levels [28]. High trough concentration of vancomycin was not significantly overall superior to low tough concentration in treatment outcome or mortality, but was associated with lower failures in the subgroup with bacteremia. Again, high trough level was strongly associated with risk of nephrotoxicity. In the third meta-analysis, 14 observational studies were included with 1677 patients with *S. aureus* bacteremia [29]. High vancomycin trough levels [≥15 mg/L] were not associated with reduced treatment failure, persistent bacteremia, or mortality, but higher AUC/MIC ≥400 was associated with reduced treatment failure, persistent bacteremia, and mortality. See Table 10.1 of summary of meta-analyses.

Individual studies published from 2014 to 2018, not included in the previous meta-analyses, were reviewed [see Table 10.1]. Nine studies [in English] were found and four were prospective observational studies with 606 adults and 387 children, and none found trough vancomycin levels were associated with outcome [30–32]. One study found that AUC/MIC ≥400 was associated with improved outcome in MRSA bacteremia [n = 117] [30], but a larger study with mixed infections [n = 334] showed no correlation of PK/PD with outcome [32]. The retrospective cohort studies included 460 adults [33, 34] and 430 children [35–38]. None of the

Table 10.1 Studies with vancomycin pharmacodynamics and outcome

	Type	Infections	Patient no.	Outcome and comments	Reference
1.	Meta-analysis	Mixed MRSA	2003	No diff. in mortality, Rx failure and trough conc.	[27]
2.	Meta-analysis	Mixed gram+	2578	No. diff. in mortality, Rx failure except bacteremia	[28]
3.	Meta-analysis	S.A. bacteremia	1677	Trough not assoc. with outcome, AUC/MIC better	[29]
4.	Prospective	MRSA bacteremia	117	Trough not assoc. with outcome, AUC/MIC better	[30]
5.	Prospective	Mixed gram+	370A/100C	Trough not associated with outcome	[31]
6.	Prospective	Mixed gram+	334	PK/PD indices not associated with outcome	[32]
7.	Retrospective	S.A. pneumonia	98	High trough did not improve outcome	[33]
8.	Retrospective	Mixed gram+ [90 MRSA]	111	High trough did not improve outcome	[34]
9.	Retrospective	MRSA bacteremia	102C	High trough did not improve outcome	[35]
10.	Retrospective	MRSA bacteremia	232C	High trough did not improve outcome	[36]
11.	Prospective	MRSA bacteremia	341C	High trough did not improve outcome	[37]
12.	Retrospective	MRSA bacteremia	46C	High trough did not improve outcome	[38]

A adults, *assoc.* associated, *C* children, *diff.* difference, *PK* pharmacokinetic, *PD* pharmacodynamics, *S.A.* S. aureus, *Rx* treatment

adult studies found low trough vancomycin concentration was associated with clinical failure. In the four pediatric studies achieving trough vancomycin concentration ≥15 mg/L was not shown to be beneficial, but trough levels <10 mg/L were associated with prolonged bacteremia compared to concentration >10 mg/L [36, 38]. Thus, in the combined recent observational studies in adults and children [retrospective and prospective] of 1851 patients, no therapeutic benefit was found to target vancomycin trough levels of 15–20 mg/L which was strongly associated with increased nephrotoxicity, but AUC/MIC ≥400 correlation to treatment success was mixed in prospective studies, better in *S. aureus* bacteremia than mixed infections.

10.1.6 Nephrotoxicity of Vancomycin

Prior to the guidelines in 2009 recommending vancomycin trough levels of 15–20 mg/L for severe MRSA infection, kidney injury from the antibiotic was very uncommon [≤5%]. However, since then there has been marked increase in vancomycin nephrotoxicity reported, up to 50% in critically ill patients with dosage >38 mg/kg/day and 57% with trough concentration >20 mg/L [39]. Several factors have been reported to be associated with nephrotoxicity including total daily dose [>4 g/day], duration >5–7 days, concomitant nephrotoxic agents, severity of illness [critical illness], obesity [>101.4 kg weight], and most consistently trough levels >15 mg/L [40, 41]. Surprisingly, several studies have reported increased incidence of acute kidney injury [AKI] with the combination of vancomycin and piperacillin/tazobactam [PT] compared to vancomycin alone. In the most recent meta-analysis on the topic 14 studies with 3549 patients were analyzed [42]. Concomitant vancomycin and PT was associated with increased AKI in adults and children primarily in studies with >50% of patients requiring ICU care. This suggests that the severity of illness is the main predictor of AKI and not necessarily the combination itself with PT.

There has been consistent reiterated data since 2009 that aggressive dosing of vancomycin to achieve higher trough levels is associated with increased kidney injury. Several reports indicated a dose-toxicity response and a linear relationship between increasing AKI and graded trough concentrations has been noted [43]. A few systematic reviews on the topic have been published. A review in 2011 of 12 studies found vancomycin nephrotoxicity was associated daily dose ≥4 g/day or 30 mg/kg and trough levels of 15–20 mg/L [44]. A subsequent review of the literature reported that nephrotoxicity was associated with dose >4 g/day, trough levels >20 mg/L, treatment with concomitant nephrotoxic agents, prolonged ICU stay, and prolonged therapy [>7 days] [45]. In a meta-analysis of 15 studies it was shown that nephrotoxicity was significantly associated with vancomycin trough concentration ≥15 mg/L than <15 mg/L [odds ratio 2.67, 95% confidence interval 1.95–3.65] [46]. In addition, there was an incremental increase in kidney injury with longer durations of treatment. Although renal function usually recovers fully after discontinuation of vancomycin, some patients require temporary or long-term hemodialysis.

Table 10.2 Studies on high vancomycin trough levels and AUC with nephrotoxicity

	Type	Infection	Patient no.	Nephrotoxicity comments	Reference
1.	Meta-analysis	Mixed MRSA	2003	Increased with ≥15 mg/L trough	[27]
2.	Meta-analysis	Mixed gram+	2578	Increased with ≥15 mg/L trough	[28]
3.	Meta-analysis	SA. Bacteremia	1677	Increased with ≥15 mg/L trough	[29]
4.	Prospective	Mixed gram+	370A/100C	Increased with ≥15 mg/L trough	[31]
5.	Retrospective	SA. Pneumonia	98	Increased with ≥15 mg/L trough	[33]
6.	Retrospective	Mixed gram+	111	Adverse events not associated with trough	[34]
7.	Retrospective	SA. Bacteremia	102C	Increased with ≥15 mg/L trough	[35]
8.	Prospective	SA. Bacteremia	341C	Increased with ≥15 mg/L trough	[37]
9.	Retrospective	MRSA Bacteremia	127	Assoc. with trough >15 mg/L, AUC > 563	[48]
10.	Prospective	Mixed gram+	252	Assoc. with trough >15 mg/L, AUC > 600	[49]

Assoc. association, *A* adults, *C* children, *SA.* Staphylococcus aureus

Moreover, even modest AKI has been associated with increased medical cost, length of hospital stay, and mortality in hospitalized patients [47]. Table 10.2 summarizes studies on nephrotoxicity and trough levels published after 2013.

10.1.7 Conclusion on Vancomycin and Future Directions

There is considerable data that higher dosing of vancomycin to achieve through levels of 15–20 mg/L does not improve outcome, has poor correlation with AUC/MIC ≥400, and is strongly associated with nephrotoxicity. This author recommends that the current guidelines on dosing and monitoring should be rescinded, as it is better to have no guideline than a bad and harmful one. Ideally this issue should be resolved by performing a randomized trial, but this may take many years to be completed. Although, high AUC/MIC appears to correlate better with outcomes than trough level, especially for MRSA bacteremia, there is inadequate data on correlation with nephrotoxicity, but two studies reported increased AKI with high AUC [48, 49], and moreover it is impractical for routine clinical care in most settings.

It is evident from multiple in vitro studies that achieving high vancomycin levels above four times the MIC [8–10 mg/L] does not increase the killing effect of vancomycin. To improve outcome with treatment of severe MRSA infections we should consider other options, i.e., use of other agents or combinations with vancomycin.

The mortality for methicillin-sensitive *S. aureus* [MSSA] bacteremia is <10% when treated with an anti-staphylococcal β-lactam agent, while the mortality for MRSA bacteremia treated with vancomycin is 20% to >30% [50]. Combination of rifampin with vancomycin appears promising to treat severe MRSA and MRSE infections, and a previous randomized trial of 93 patients with nosocomial MRSA pneumonia showed improved outcome with adding rifampin than vancomycin alone [51]. A recent large multicenter, randomized, double-blind, placebo-controlled trial showed adjunctive rifampin did not improve outcome in *S. aureus* bacteremia with 758 participants [52]. However, only 47 [6%] had MRSA infections and, thus, does not disprove the benefit of adding rifampin to vancomycin for MRSA infections. Hence, large randomized trials are warranted using adjunctive rifampin with vancomycin or other agents in severe MRSA infections, including bacteremia and endocarditis.

Interestingly, in vitro pharmacokinetic/pharmacodynamics studies reported synergy of certain β-lactam agents with vancomycin against MRSA with optimal bactericidal effect at 48 h [53, 54]. Animal models have also shown synergy of vancomycin with β-lactam agents against MRSA infection [55]. Two retrospective cohort studies have been reported in patients with MRSA bacteremia and the effect of combined β-lactam and vancomycin versus vancomycin alone. The combination in the first study [n = 80] found microbiological eradication was greater with the combination [96%] than single agent [80%], p = 0.021 [56]. The second study [n = 110] found that combination therapy was the only variable in multivariate analysis that decreased treatment failure [57]. A pilot randomized controlled trial [n = 60] of vancomycin with flucloxacillin compared to vancomycin alone showed the combination shortened the duration MRSA bacteremia, but was underpowered to assess outcome [58]. Clearly larger multicenter, randomized, controlled trials are needed in the near future.

10.2 The Need for Intravenous Antibiotics in Osteomyelitis

10.2.1 Background on Osteomyelitis

Osteomyelitis, infection of the bone, is uncommon in healthy children and adults and acute osteomyelitis is estimated to occur in about one in 100,000 children per year in high-income countries and much more in low-income countries [59], but the prevalence or incidence in adults is not well delineated. Osteomyelitis can be classified as acute, <2 weeks; subacute 2 weeks to 3 months duration; and chronic with duration of illness >3 months. The source of the infection can be hematogenous in origin [most common in children], from contiguous skin/soft tissue infection [most commonly diabetic foot infection in adults] to post-surgical following wound infection [increasingly recognized in adults following prosthetic insertion]. Historically osteomyelitis has been treated with prolonged antibiotics, 4–6 weeks for acute infection and 3 months or more [plus surgical drainage and debridement] for chronic

infection. Intravenous antibiotic [IV] for at least 4 weeks was adopted as the standard care empirically for many years until recently.

10.2.2 Pediatric Studies of Acute Osteomyelitis

One of the first studies to evaluate early transition from parenteral to oral antibiotics in acute staphylococcal osteomyelitis in children was published in 1997 [60]. This prospective study of 50 children, showed oral antibiotics for 3–4 weeks after 3–4 days parenteral therapy was just effective as total parenteral antibiotics. The same group of investigators subsequently conducted a prospective randomized study of acute hematogenous osteomyelitis [89% due to *S. aureus*] in 131 children [61]. All the patients received IV antibiotics for 2–4 days, 67 children received 20 days of oral agent, and 64 children received 30 days of either clindamycin or a first-generation cephalosporin. At 1 year follow-up all patients recovered entirely with one mild sequel in each group. Although this study was not a direct comparison of mainly oral therapy versus only IV treatment, it demonstrated two points: firstly, oral antibiotic after brief parenteral therapy is very effective and safe in pediatric acute osteomyelitis; secondly, 3 weeks treatment appears to be adequate once the C-reactive protein [CRP] is <20 mg/L [61]. A subsequent systematic review of the topic was published in 2002 [62] and concluded that short courses of parenteral antibiotics [<7 days] followed by oral therapy was very effective [95.2%] for acute osteomyelitis of childhood.

Since this review, there have been several prospective and retrospective studies as well as reviews on this issue in the pediatric literature. Two large retrospective studies have been reported with a combined total of 4029 patients with acute osteomyelitis: 2076 children receiving prolonged parenteral therapy and 1952 mainly oral therapy [63, 64]. Treatment failure was similar with the two forms of treatment, 5–6% for total parenteral therapy and 4–5% in the mainly oral therapy. A systematic review of 12,000 case of pediatric acute osteomyelitis in 2012 [65] and a recent overview in 2016 [66] came to the same conclusion, and noted that there was increasing evidence that prolonged parenteral therapy can do more harm than good.

10.2.3 Adult Osteomyelitis

10.2.3.1 Background

Traditionally osteomyelitis in adults have been classified as acute or chronic depending on the course and histology and imaging findings, but as noted in a review in 1970 [67] the features are often over-lapping and not well defined and the onset difficult to delineate. However, it may still be reasonable to consider adult acute osteomyelitis as having onset within 3 months and chronic >3 months. Unlike

pediatric osteomyelitis, bone infections in adults are more heterogeneous and complicated with presence of vascular disease [diabetic foot infection], or presence of foreign materials such as prosthetic joints, rods, plates, and screws for internal fixation of fractures. Furthermore, acute hematogenous osteomyelitis is very uncommon and primarily involves the spine. Although acute vertebral osteomyelitis is most commonly due to *S. aureus*, the microbial etiology varies on the predisposing condition, i.e., mixed coliforms, staphylococci, streptococci, and anaerobes for diabetic foot osteomyelitis; skin bacteria [coagulase-negative staphylococci {CoNS}, diphtheroids], *S. aureus* and occasionally Gram-negative bacilli with prosthesis. Thus data on therapeutics of adult osteomyelitis have been small retrospective studies with various antibiotics, depending on the etiological organisms and usually of low quality.

10.2.3.2 Treatment of Adult Osteomyelitis

Most acute osteomyelitis in the absence of prosthesis, foreign material, abscess, or vascular disease can be treated with antibiotics alone for 6 weeks. Chronic osteomyelitis, presence of abscess, tissue necrosis, and presence of foreign material usually require surgery and often longer course of therapy. Although there is no proof or good evidence that parenteral antibiotics are needed for most of the course, this has been the usual practice. There has been a misconception that high serum levels are needed with IV antibiotics to achieve adequate bone penetration/concentration to treat osteomyelitis, especially with β-lactam agents. A recent review of antibiotic bone penetration noted that most oral antibiotics including cloxacillin, amoxicillin, amoxicillin-clavulanate, doxycycline, rifampin, quinolones, clindamycin, cephalosporins, fusidic acid, and trimethoprim/sulfamethoxazole [TMP/SMX] provide adequate bone concentrations above the MIC or the breakpoint concentration for susceptibility [68]. Intravenous antibiotic is commonly used unnecessary in high-income and low-income countries, and prolonged IV therapy is expensive and associated with complications such as local phlebitis, thromboembolic disease, extravasation injury, and local and systemic infections including bacteremia and candidemia [69].

10.2.3.3 Studies on Oral Antibiotics in Adult Osteomyelitis

Few prospective or randomized studies have been performed in adult osteomyelitis, most of which were small and underpowered until most recently. Even the combined data of oral antibiotic treatment including retrospective and prospective studies of osteomyelitis in adults are much less robust than in children. A few systematic reviews of antibiotic therapy for adult osteomyelitis have been published over the years.

In 2001, a systematic review and meta-analysis analyzed 22 trials with only 927 patients, most with small sample size and low quality, reported no significant differ-

ences in long-term results were found between IV antibiotics and oral agents, especially rifampin-ciprofloxacin combination [70]. An overview of antibiotic treatment of osteomyelitis reviewed pediatric and adult data and concluded that there was inadequate data to determine the best agents, route, or duration of therapy [71]. Studies on vertebral osteomyelitis suggest parenteral antibiotics and oral quinolones [especially for Gram-negative bacilli] are similar, but increased resistance of staphylococci against quinolones render these agents unreliable [72]. Although it was suggested that oral β-lactam agents should not be used because of poor bioavailability, this can be overcome by increasing the dose [personal experience]. Moreover, oral β-lactams have been used with very good response in pediatric acute osteomyelitis and there is no biological reason that they should not be effective in adults.

A review of therapy for chronic osteomyelitis in adults was published in 2012 and concluded that success rates were similar for parenteral versus oral therapy, with fewer studies published on prolonged IV therapy [73]. Combined therapy with rifampin had shown improved response in animal models, retrospective studies and one randomized trial in orthopedic implant-related staphylococcal osteomyelitis [73, 74]. The optimum duration of antibiotic therapy was not well defined, although 4–6 weeks is commonly used after surgery, and surgical resection of necrotic and infected bone with antibiotics appears to increase the cure rate of chronic osteomyelitis, but not always required to obtain cure. Although oral quinolones appears to be quite effective for susceptible Gram-negative bacilli osteomyelitis, there was increasing reports of relapse and resistance for Gram-positive cocci infections. The report suggested that TMP/SMX or clindamycin may be preferable for staphylococcal infections with alternatives including doxycycline and linezolid [73]. A Cochrane review of antibiotic treatment of chronic osteomyelitis in 2013 came to similar conclusion regarding oral versus parenteral therapy, but included only eight small trials with 282 participants because of low quality [75]. But there was insufficient evidence to arrive at any conclusion regarding other aspects of treatment such as surgery, duration of therapy, or choice of oral antibiotics.

Diabetic foot osteomyelitis is probably the most common osteomyelitis seen in adults and represents a challenge to treat in view of underlying vascular disease and peripheral neuropathy with chronic recurrent plantar ulcers, which predispose to recurrent infection. Moreover, the microbial etiology is frequently mixed, although *S. aureus* is the single most common pathogen and surgery is commonly indicated for debridement, drainage of abscess, and partial amputation of digits or forefoot. Oral antibiotic for diabetic foot osteomyelitis data is sparse and mostly of retrospective studies. In a study published in 2006, 79 patients with 94 episodes of osteomyelitis were treated with 2–4 oral antibiotics, with or without brief parenteral therapy, showed 80.5% remission after very unusually long duration [76]. Guidelines had recommended ≥3 months of antibiotics in absence of surgical resection and 6 weeks after surgery [77]. However, in a small randomized, multicenter trial results of 6 weeks [$n = 20$] versus 12 weeks [$n = 20$] antibiotic therapy were similar without bone resection [78]. In this study oral antibiotics were used for the entire period or after 5–7 days parenteral therapy. One of the largest antibiotic trial in diabetic foot

infection [$n = 371$] included patients with mainly skin/soft tissue infections with 77 cases of osteomyelitis; randomized to receive linezolid with or without aztreonam or aminopenicillin/β-lactamase inhibitor, given IV [7.8–10.4 days] then orally for about 2 weeks, cure rates were similar for IV vs oral therapy, but this was not the primary objective of the study and cure rate of osteomyelitis was only 60–65% [79].

The largest and most robust study on oral versus parenteral antibiotics in bone and joint infection was most recently published. This multicenter, randomized trial enrolled 1057 participants [527 in each group] to receive primarily IV antibiotics versus oral antibiotics ≥6 weeks [after 7 days of parenteral therapy] with follow-up at 1 year, and no difference in outcome was found, treatment failure 13.2–14.6% [80]. The patients had complex orthopedic infections with 60.6% metalware-related infections, 7.6% treated without surgery. Of the metal-implant-related infections [excluding joint prosthesis] 167/414 [40.5%] had removal of the implant and 247 [59.7%] had debridement and retention of the implant. It is unclear from the data provided whether or not those with implant retention were primarily long-term, stable implants in the spine, which in clinical practice are usually retained [personal experience]. In the 225 patients with prosthetic joint infection, 135 [60%] had device removal and 90 [40%] had one stage revision. The most commonly used IV antibiotics were glycopeptides [vancomycin and teicoplanin] and cephalosporins and a variety of oral agents [based on the microbiological results, susceptibility, and bioavailability]. Of note, adjunctive oral rifampin was used in 28.7% of patients on parenteral therapy and 69% of those on oral therapy, but outcomes did not vary with rifampin use [although the trial was not designed for this assessment]. The most commonly used oral agents included quinolones [21.5%], penicillins [8.1%], tetracyclines [doxycycline, 5.8%], macrolides/clindamycin [7.5%], and combination with other agents [excluding rifampin] [9.6%]. The trial did not show any difference between the various oral antibiotics, but it was underpowered and not designed for this purpose [80]. The median duration of therapy in the IV group was 78 days and 71 days in the oral group. The microbial etiological organisms were similar between the groups, overall MSSA [37.7%], CoNS [27.1%], Streptococcus species [14.5%], Pseudomonas species [5.1%], and other Gram-negative bacilli [15.5%] [80].

A more recent prospective, observational study of early spinal infection in 85 patients, 74 [87.1%] with instrumented spinal fusion, reported that 10 days IV antibiotics followed by oral agents [most commonly levofloxacin, rifampin, and amoxicillin] for a total of 6 weeks after surgical debridement and irrigation was successful in 91.8% at 1 year [81]. Of note is that when surgical devices and bone graft were present, they were carefully washed with a surgical brush and pulsed saline and kept in place. This may be important in the outcome of retained devises as these procedures likely aid in the removal of biofilms, whereas routine debridement and irrigation would be less effective. Another recent observational multicenter, retrospective study of prosthetic joint infections [87 hip or knee] treated by debridement and implant retention [DAIR], primary assessment was to compare the efficacy of 6 weeks compared to 12 weeks therapy [82]. However, initial IV therapy was used for a mean of 10–13 days followed by oral antibiotics [69% in both groups received

rifampin in combination], and the outcomes were similar with 69% of patients free of infection at a mean follow-up of 4.3 years.

10.2.4 Selection of Oral Antibiotics for Treatment of Osteomyelitis

There is no evidence based on clinical trials or observational data to determine the most suitable oral antibiotic for treatment of osteomyelitis. The clinical decision to use any specific agent should be guided by microbiological identification and susceptibility, oral bioavailability, underlying comorbidities [i.e., renal function], allergies, drug interactions, age with risk of adverse effects, and plausible biological effects. The advantages and disadvantages of various oral agents for osteomyelitis are discussed (see Table 10.3).

Rifampin is a broad-spectrum antibiotic, with bactericidal activity and high potency against staphylococci in vitro and in biofilm environment, even in the sessile phase of growth, with very good bioavailability and good intracellular penetration into many tissues including bone [83]. It is not used alone as rapid resistance readily develops. Rifampin is usually well tolerated but occasionally causes liver disturbance, nephritis, and rarely cytopenias. The main disadvantages are drug interactions, as it is a potent inducer of the cytochrome P450 oxidative pathway [84], and resistance still can develop even when used in combinations. Rifampin is used extensively in combination with various antibiotics for implant-related staphylococcal infections, including MSSA, MRSA, MRSE, or CoNS, especially for orthopedic device-related infections [ODRI]. Although several animal studies had shown that adjunctive rifampin was more effective than monotherapy for implant-related staphylococcal infections, human studies have shown mixed results varying from 55% to 100% good outcome [85]. Based on in vitro and in vivo studies rifampin-combinations are most effective for young early biofilms with low bacterial load, and the best results in clinical studies in ODRI are in patients with short duration [<1 month] of symptoms with intact skin and no sinus tract [85]. The clinical benefit of rifampin in various combinations [most often with a quinolone] has mainly been documented from one small randomized trial [74] and a large multicenter, retrospective study in ODRI [86]. A concern with rifampin is the development of resistance rapidly which occurred in 27% of cases of *S. aureus* native valve endocarditis treated with adjunctive rifampin [87]. Hence, for implant-associated infection with bacteremia it has been suggested to start rifampin after 5 days of antibiotic therapy to reduce the high bacterial load and reduce risk of resistance. In patients with ODRI treated with adjunctive rifampin, persistence of staphylococci was associated with rifampin resistance in 10% [86]. New concerns have been raised that rifampin resistance with rpoB gene mutation can lead to cross resistance to vancomycin and daptomycin in *S. aureus* [88]. Use of rifampin in ODRI should be used after extensive surgical debridement with retention of the

implant, preferably with liner exchange, one stage arthroplasty and although not recommended for two-stage exchange [>6 weeks] [85], insertion of a joint spacer is a risk for recurrent biofilm infection and rifampin may be indicated. There is no guideline on the most appropriate dose of rifampin for adjunctive therapy in *S. aureus* infection, and doses in studies vary from 300 mg to 600 mg twice daily. However, the dosing should be guided by the weight of the patient in order to achieve sufficient blood and tissue concentration.

Quinolones [ciprofloxacin, levofloxacin, and moxifloxacin] were commonly used in studies with rifampin for ODRI. The advantages of these agents include broad-spectrum activity, good bioavailability and bone penetration, low pill burden, and perceived good safety profile in past years. Increasing resistance of staphylococci to fluoroquinolones has been reported in the last several years with failures and relapse on combination with rifampin. In a report in 2016, ciprofloxacin resistance was found in 14% of MSSA, 85% of MRSA, and 46% of CoNS in patients with bone and joint infections [89]. Quinolones still remain a good choice for Gram-negative bacilli osteomyelitis, as the choice for oral antibiotics are limited. Prolonged use of quinolones is of concern, especially for elderly patients, because of serious adverse events. Ciprofloxacin and other quinolones are high risk agents for develop-

Table 10.3 Oral antibiotics for osteomyelitis after brief parenteral therapy

Agent	Bioavailability	Bone conc.	Activity	Advantage	Disadvantage
Rifampin^{++}	Very good	Very good	Potent anti-staph.	Biofilm penetration.	Resistance easy, drug interactions
Quinolones	Very good	Good	Broad spectrum	Easy dosing	↑ side-effect
					↑ staph. resistance
Clindamycin	Very good	Good	Gram-positive cocci, anaerobes	Few side effects	↑ *C. difficile* colitis
Dicloxacillin	Good [≈70%]	Good	MSSA, strep.	C. difficile rare	Multiple oral dosing
Cephalexin	Very good	Good	MSSA, strep.	Few side effects	Multiple oral dosing
Fusidic acid	Very good	Good	MSSA, MRSA	Few side effects	Multiple dosing, use mainly with rifampin
Linezolid	Very good	Good	MSSA, MRSA, CoNS	Easy dosing	Expensive, serious side effects with long course
TMP/SMX	Very good	Good	MSSA, MRSA, CoNS	Easy dosing	↑ side effects in elderly
Doxycycline	Very good	Accumulate in bone	MSSA, MRSA, CoNS	Easy dosing, bio. effect on bone	↑ GI upset in elderly

bio. biological, *GI* gastrointestinal, *penetr.* penetration, *staph.* staphylococci, *strep.* streptococci, $^{++}$use in combination only

ment of severe, recurrent *Clostridium difficile* colitis, which is increased in the elderly with prosthesis, multiple comorbid illness [example renal failure] and receiving proton-pump inhibitor [PPI]. Achilles tendinitis and rupture were recognized as rare complications in the elderly and patients with rheumatoid arthritis, as well as drug interactions with a several drugs metabolized by CYP1A2 [theophylline, clozapine, and olanzapine]. However, in the last few years there have been multiple black-box warnings from the FDA of serious drug reactions to the quinolones, with recommendations to administer them mainly when no suitable alternatives are available, especially for prolonged use. These serious adverse reactions include peripheral neuropathy that may occur soon after initiation and may be irreversible in some patients; central nervous system effects [hallucinations, depression, anxiety, severe headaches, insomnia, confusion, psychotic reactions and aseptic meningitis]; arthropathy and myalgia in pediatric patients and worsening of myasthenia gravis; prolongation of the QT interval and arrhythmia; photosensitivity and phototoxicity; hypoglycemia [mainly in subjects on oral hypoglycemic agents]; and most recently increased risk of ruptures or tears in the aorta of certain patients [elderly patients with atherosclerotic diseases, hypertension, Marfan syndrome and Ehlers-Danlos syndrome] [https://www.fda.gov/Drugs/Drugsafety/ucm51130.htm]. The quinolones have biological effects that can explain some of these adverse effects and theoretically it could be argued that they should be avoided in patients with any bone and joint diseases. The fluoroquinolones cause change in extracellular matrix, signaling proteins, increase of matrix metalloproteinase [especially MMP-3] and the apoptosis marker caspase-3, which causes decrease type 1 collagen [90, 91] and are likely the mechanisms for the tendinopathy, muscular-skeletal, and vascular effects. Pre-clinical studies of ciprofloxacin in young dogs showed lameness with permanent lesions and erosions of cartilage in weight bearing joints [FDA report on drug safety].

Oral β-lactam agents are not commonly used in studies in adult osteomyelitis but pediatric data support their use for hematogenous *S. aureus* [MSSA] osteomyelitis, and there is no valid reason not to use these very safe agents in adults. First-generation cephalosporin and antistaphylococcal penicillins can be used and are effective in limited adult data in osteomyelitis, and in combination with rifampin for ODRI, and are recommended by guidelines as possible choices [92]. They are suitable agents for MSSA and streptococcal infections, but skin bacteria such as CoNS and Corynebacterium species are commonly resistant to the β-lactam agents, limiting their use in prosthetic joint infections. Besides allergic reactions, these agents are safe with low risk for *C. difficile* colitis [rare with cloxacillin] or low-moderate for cephalexin. High oral dose of cloxacillin or phenoxymethyl penicillin [penicillin V] with probenecid has been used in the past for chronic *S. aureus* osteomyelitis with very good response in 191 patients [93]. Oral cloxacillin is only 50% absorbed, but dicloxacillin is better absorbed [about 70%] and cephalexin 90–100% absorbed [94]. A disadvantage in using the these agents is the need for dosing four times a day and high pill burden associated with high doses to achieve high blood levels and good bone penetration, which may result in intolerance. Amoxicillin-clavulanate [clavulin] is a broad-spectrum antibiotic suitable for diabetic foot osteomyelitis, as

it covers MSSA, streptococci, anaerobes, and community acquired coliforms. The bioavailability is good and it provides good bone penetration, moreover, the higher dose pill 'clavulin-875' can be dosed twice daily. The broader antimicrobial activity is also a disadvantage, as this leads to greater risk of diarrhea and *C. difficile* colitis than amoxicillin and cephalexin.

Other oral antibiotics that have been used for osteomyelitis with or without rifampin [including ODRI] include TMP/SMX, clindamycin, fusidic acid and linezolid. The latter agent is suitable for MRSA and MRSE infection and provide good bone levels, but should be reserved and used when no suitable other oral agent is available. It is very expensive despite being generic and has significant hematological side effects and risk of neuropathy when used for more than 2 weeks. Also there is increasing reports of linezolid-resistant *S. aureus* and widespread use will drive this trend. Clindamycin was used in some studies and retrospective reports of osteomyelitis including ODRI, as the oral absorption is very good and it provides adequate bone concentration. However, ≥24% of MSSA, ≥44% of CoNS and ≥76% of MRSA are resistant to clindamycin [89]. Clindamycin resistant *S. aureus* continue to rise globally and as high as 97% in an area in the US [95]. The main disadvantage of clindamycin for prolonged use is the high risk of *C. difficile* colitis which is often recurrent and refractory with continued use of antibiotics. TMP/SMX is broad-spectrum agent with good activity against Gram-negative bacteria and staphylococci, including MSSA, most MRSA and CoNS and has been used with rifampin for ODRI in a few reports. TMP/SMX has been shown in a randomized trial to result in similar response/failure as vancomycin for serious MRSA infection [36% bacteremia], but noninferiority could not be proved [96]. The disadvantages of prolonged use of TMP/SMX in the elderly include greater risk of side effects including renal impairment, hyperkalemia, and occasionally bone marrow suppression. Sudden death in the elderly has been reported with TMP/SMX, probably due to hyperkalemia, especially in patients receiving inhibitors of the angiotensin-renin system or spironolactone [97, 98]. Fusidic acid is primarily used in Europe for bone and joint infections due to staphylococci and has been touted as a good option with rifampin for ODRI, as resistance is low in MSSA [3%], MRSA [8%] and higher with CoNS [26%] [89]. There are several reports of fusidic acid use in chronic osteomyelitis, most often in combination with rifampin and other agents, for decades in Europe. Low level resistance can readily occur with monotherapy and co-administration with rifampin can lower its blood level [through induction of CYP3A4] and result in both fusidic acid and rifampin resistance [99]. Fusidic acid is usually well tolerated except for gastrointestinal discomfort, diarrhea, and headaches, uncommon skin reactions, and rarely granulocytopenia and thrombocytopenia [100].

Tetracyclines use for osteomyelitis is sparse in the literature and in the large randomized trial only 5.8% of patients were treated with doxycycline [80]. Yet, tetracyclines [especially long-acting agents] have some of the most suitable biological and pharmacodynamics properties for treatment of bone and biofilm infections. Tetracycline has broad spectrum of activity against Gram-positive, Gram-negative, and atypical bacteria. Doxycycline and minocycline have advantage over other

members of the tetracycline family with almost complete absorption and improved serum half-life [18–24 h] and good penetration in most tissues [101]. The long-acting tetracycline have very good in vitro activity against staphylococci species including MSSA, MRSA/MRSE, and CoNS, even when there is resistance to the short acting tetracycline [102]. Doxycycline or minocycline has been used in MRSA uncomplicated skin and soft tissue infections with 96% response in 90 treated patients [103]. However, in selective strains of *S. aureus* from complicated skin and soft tissue infections from three clinical international studies of tigecycline, tetracycline resistance genes were found in 2.5–16.1% of MSSA and 11.9% to 46.2% of MRSA with marked regional variation [104]. In a survey of resistance trends and in vitro activity of 17 antimicrobials against Gram-positive bacteria collected from 15 sites in Germany from 2005 to 2009, doxycycline resistance to MSSA declined from 3.4% to 0.7%, remained stable for MRSA 5.8% to 4.6%, and declined from 10.1–12.3% to 5.9–6.1% for CoNS [105]. Susceptibility of staphylococci collected in 2015 at my university teaching hospital showed 91% of 293 strains of CoNS were tetracycline susceptible and 93% of 330 *S. aureus* [MSSA and MRSA] were tetracycline susceptible [unpublished data].

Tetracycline [and its derivatives] is a bone-seeking agent that has been used in the past as a useful marker for bone resorption studies. It exhibits bone uptake and release kinetics similar to other bone-seeking agents such as the bisphosphonates [106]. Tetracycline is deposited in metabolically active bone by chelating with calcium and 3–6% of the dose [up to 80% penetration] is retained and accumulates in the bone, and in animal studies after a single dose 100% may be excreted in 70 days ['slow compartment'] [106]. Doxycycline and minocycline have anti-inflammatory properties at sub-microbial concentration by inhibiting matrix metalloproteinases [MMP] and reduce periodontal breakdown and extra-oral bone loss [107]. These two long-acting agents are among the most effective MMP inhibitors of the tetracycline analogues used to ameliorate the effect of osteopenia associated with inflammatory arthritis [108, 109]. Besides the anti-MMP activity, the positive protective effects of tetracyclines on bone and cartilage include activation of osteoblasts and inhibition of osteoclastic activity [110, 111]. Tetracycline derivative has been shown to positively influence bone integrity through inhibition of collagen breakdown in arthritis animal model [112]. The calcium binding of tetracycline in bone also may be of beneficial effect in inhibiting biofilm formation, a major pathogenic mechanism in implant-mediated infections and probably in chronic osteomyelitis. In an in vitro study, a hydrophobic coating of calcium bound minocycline allowed sustained release of the drug to provide effective antibiotic and anti-inflammatory effect for inhibition of biofilm formation [113].

The long-acting tetracyclines are usually well tolerated and the most common side effects are gastrointestinal disturbances which can be reduced by taking with food and appears more frequently in the elderly [personal experience]; and less commonly are esophagitis, photosensitivity, pediatric teeth discoloration [contraindicated in children], and rarely hepatotoxicity, hypersensitivity, and idiopathic intracranial hypertension [114]. Minocycline is more likely to cause central nervous system side effects than doxycycline such as dizziness, lack of concentration, ataxia,

vertigo, tinnitus with weakness, nausea, and vomiting. Thus doxycycline is more commonly used. A distinct advantage of doxycycline for long-term use, especially compared to quinolones and other broad-spectrum antibiotics, is the decreased risk of *C. difficile colitis* compared to other antibiotics [115].

Doxycycline is unnecessarily underused in studies for bone and joints infections and large prospective and comparative, randomized studies are warranted. However, the author has extensive experience with doxycycline in osteomyelitis and ODRI with mainly staphylococci [MSSA, MRSA, and CoNS], Corynebacterium species, *Propionibacterium acne,* and occasionally Gram-negative bacilli over the last 15–20 years with very good response. Most commonly oral doxycycline was combined with rifampin for ODRI after variable periods of parenteral therapy for 1–4 weeks, but occasionally oral therapy has been used from the outset.

10.2.5 Conclusion on Oral Antibiotics in Bone and Prosthetic Joints Infection

Based on the combined data from randomized trials, observational prospective and retrospective cohort studies there is substantial data to support the use of oral antibiotics for most of the course, if not the entire course, for bone and joint infections, including those with prosthesis or hardware. Long-term IV antibiotics for these infections should be considered passe', expensive, and unnecessary both in children and adults. Furthermore, there is now convincing data that joint prosthesis and spinal hardware infection can be treated with short courses of mainly oral antibiotics for 6 weeks with retention of the hardware/prosthesis after special surgical drainage, irrigation, and methods to remove biofilm. However, these prosthetic material should be stable, treated early after onset [<3 weeks after onset], not associated with sinus and resistant bacteria such as MRSA, where relapse or failure is greater [81, 82]. Although there is inadequate data to recommend any specific oral agents, combination with rifampin appears to be optimal for staphylococcal infections with prosthesis/hardware.

10.3 Oral Antibiotics for Bacterial Endocarditis

10.3.1 Background on Infective Endocarditis

Infective endocarditis [IE] is a rare but serious infectious disease which appears to be increasing in recent years, from 9.3 per 100,000 in 1998 to 15 per 100,000 of the US population in 2011 [116]. This increase appears to be largely related to an increase in healthcare–associated IE [34% of cases] and increase IV-drug abuse [IVDA] IE [117]. The change in source of infection has resulted in a shift of the

frequency of etiologic organisms, with *S. aureus* accounting for 40% of the isolated bacteria as the single commonest cause, although 70% of the cases are community acquired.

10.3.2 Treatment of Infective Endocarditis

Treatment of IE is complex and parenteral antibiotics for 4–6 weeks have been the standard internationally with or without surgery for cardiac valve replacement with prosthetic valves. Bactericidal antibiotics, singly or in combination, are considered essential to sterilize cardiac vegetations which are considered a form of biofilm infection [118]. Prolong IV antibiotics is expensive and associated with multiple complications in hospital or for home parenteral therapy. This was first recognized as a problem in IVDA, as the patients frequently discharge themselves prematurely and home parenteral therapy was inconvenient to arrange or provided a means for illicit drug injections. Thus, one of the earliest randomized trials to assess oral antibiotics versus IV antibiotics was reported in 1996 in 85 IVDA with right-sided staphylococcal IE, using oral ciprofloxacin with rifampin compared to IV oxacillin or vancomycin for 28 days in hospital. The cure rates were similar, 89% and 90%, but drug toxicity was significantly more common in the parenteral treated group, 62% vs 3%, $p < 0.0001$ [119].

The first major study on left-sided IE treated with oral antibiotics, randomized 30 patients to receive IV ceftriaxone for 4 weeks versus 2 weeks of IV ceftriaxone followed by 2 weeks of oral amoxicillin [4 g daily] with 100% cure rate in both groups [120]. However, this trial was too small to exclude significant difference between the treatment groups and was a preliminary exploratory study. Seven observational studies evaluating the use of oral β-lactams [five], oral ciprofloxacin with rifampin [one], and linezolid [one] for treatment of IE [mixture of right- and left-sided] reported cure rates of 77% to 100% [121]. In a large cohort of IE treated in France, 6% with right-sided IE and 23% with prosthetic valves, 214 patients [50%] were switched to oral antibiotics at a median of 20 days and compared to patients treated with full parenteral therapy, there was no difference in mortality, relapse, or reinfection [122]. The oral antibiotics included amoxicillin alone in 109 cases or a combination of clindamycin, quinolone, rifampin and/or amoxicillin in 46 cases.

10.3.3 Recent Randomized Trial of Partial Oral Therapy in Endocarditis

The largest randomized, noninferiority, multicenter trial of partial oral versus IV antibiotic treatment of IE was recently published. This trial [POET] from Denmark included 400 adults with stable left side IE due to streptococcus [49%], *Enterococcus*

faecalis [24.3%], *S. aureus* [21.8%], and CoNS [5.8%] [123]. Prosthetic valve IE was present in 107 patients [26.8%] and pacemaker IE in 14 patients [3.5%]. All patients received parenteral therapy for at least 10 days, but the median time from diagnosis to randomization was 17 days with additional 19 days for the IV group [total 36 days] and 17 days with additional 17 days [total 34 days] for the oral group. The oral regimens consisted of two antibiotics from different classes with different mechanisms of action and different mode of metabolism, thus, could be additive or synergistic microbial effective but this was not the aim of the combination. The composite outcome [all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia] after 6 months were no different between partial IV or complete parenteral antibiotics [12.1% in IV vs 9.0% in oral group] [123]. Long-term outcomes after a median of 3.5 years showed no difference between the two types of treatment, but increased composite outcomes in both groups [38.2% in IV vs 26.4% in oral group] [124]. The oral antibiotic combinations from the POET trial are shown in Table 10.4.

10.3.4 Conclusion on Oral Antibiotics in Infective Endocarditis

Based on the accumulative data and recent randomized trials total parenteral antibiotics for 4–6 weeks is unnecessary for stable patients with right side and left side IE. This is particularly applicable for IVDA patients who frequently discharge themselves from hospital prematurely and home parenteral therapy carries a great risk of catheter abuse and access for overdosing with opioids. The major concern in IVDA subject is their compliance with completion of oral therapy and regular clinic follow-up. Partial oral therapy for left side IE should be cost-effective and reduce the risk of long-term IV catheter, but patients should be followed in the clinic weekly to assess for heart failure, need for cardiac surgery, and intolerance of oral antibiotics and the need for substitutions of oral antibiotic. Even though the POET trial did not show a difference in adverse events between the two forms of therapy it may have been underpowered for this aspect.

10.4 Issues in the Treatment of *S. aureus* Bacteremia

10.4.1 Background of S. aureus *Bacteremia*

S. aureus bacteremia [SAB] is a serious and common infection that appears to be increasing in industrialized countries due to increasing use of long-term or permanent catheters for hemodialysis and other purposes and increasing use of prosthesis and artificial implants. In Denmark, the incidence of SAB increased from three per

Table 10.4 Oral regimens used in the POET trial

A. Penicillin and methicillin-sensitive *S. aureus* and CoNS	E. Streptococci MIC <1 mg/L penicillin
1. Amoxicillin 1 g × 4 and fusidic acid 0.75 g × 2	1. Amoxicillin 1 g × 4 and rifampin 0.6 g × 2
2. Amoxicillin 1 g × 4 and rifampin 0.6 g × 2	2. Linezolid 0.6 g × 2 and rifampin 0.6 g × 2
3. Linezolid 0.6 g × 2 and fusidic acid 0.75 g × 2	3. Linezolid 0.6 g × 2 and moxifloxacin 0.4 g × 1
4. Linezolid 0.6 g × 2 and rifampin 0.6 g × 2	
B. Methicillin-sensitive *S. aureus* and CoNS	F. Streptococci MIC ≥1 mg/L penicillin
1. Dicloxacillin 1 g × 4 and fusidic acid 0.75 g × 2	1. Linezolid 0.6 g × 2 and rifampin 0.6 g × 2
2. Dicloxacillin 1 g × 4 and rifampin 0.6 g × 2	2. Moxifloxacin 0.4 g × 1 and rifampin 0.6 g × 2
3. Linezolid 0/6 g × 2 and fusidic acid 0.75 g × 2	3. Moxifloxacin 0.4 g × 1 and clind. 0.6 g × 3
4. Linezolid 0.6 g × 2 and rifampin 0.76 g × 2	
C. Methicillin-resistant CoNS	
1. Linezolid 0.6 g × 2 and fusidic acid 0.75 g × 2	
2. Linezolid 0.6 g × 2 and rifampin 0.6 g × 2	
D. *Enterococcus faecalis*	
1. Amoxicillin 1 g × 4 and rifampin 0.6 g × 2	
2. Amoxicillin 1 g × 4 and moxifloxacin 0.4 g × 1	
3. Linezolid 0.6 g × 2 and rifampin 0.6 g × 2	
4. Linezolid 0.6 g × 2 and moxifloxacin 0.4 g × 1	

clind. clindamycin, *CoNS* coagulase-negative staphylococci

100,000 person-years in 1957 to 20 per 100,000 person-years in 1990 [125]. This was largely attributed to nosocomial and healthcare-associated infections. In developed countries the population incidence ranges from ten to 30 per 100,000 person-years [126] and up to 38.2 per 100,000 person-years in parts of the US [127]. The all-cause mortality of 20% has remained unchanged since the 1990s and methicillin resistance which has been increasing is an independent risk factor of mortality [128, 129]. Most recent studies from Europe have found that community acquired SAB only account for 26–27.6% of cases whereas healthcare-associated and nosocomial infection account for 63.2 to 72% [130, 131]. Pooled data from five international observational studies of 3395 cases of SAB showed the crude 14 and 90 day mortality of 14.6% and 29.2%, respectively, were independently related to age, MRSA, nosocomial acquisition, IE, and pneumonia, but strongly associated with an unidentified focus [131]. Other risk factors for mortality include multiple comorbidities, disease severity [septic shock] and primary bacteremia.

A major concern of SAB, especially in patients with no clinical source or focus, is the development of IE and metastatic infection of bone and joints. The frequency of IE in SAB varies according to studies from 10 to 46% depending on the patient population [i.e., IVDA, underlying cardiac valve disease], but in the large prospective study of almost 3400 patients IE occurred in 8.3% and metastatic osteoarticular infection was identified in 13.4% [132]. Although skin and soft tissue infections [including surgical wounds] can cause transient bacteremia [14.8% of the SAB] [132], they are rarely associated with subsequent risk of IE.

10.4.2 Concerns and Controversies in the Management S. aureus *Bacteremia*

SAB traditionally has been classified as uncomplicated without any evidence of deep or metastatic infection and complicated with IE or deep metastatic infection [cause or consequence], and treatment for uncomplicated SAB was recommended with 2 weeks parenteral therapy and complicated SAB with 4–6 weeks [133, 134]. Since IE may be missed clinically, it was recommended that transesophageal echocardiography [TEE] should be performed before classifying patients as uncomplicated SAB. However, TEE is an expensive invasive test which is not available in all medical centers and is frequently not performed in clinical practice. Cardiologist who performs echocardiogram will usually do a transthoracic echocardiogram [TTE] and only if suspicious of IE or abnormal would then proceed to TEE [personal experience].

There is no randomized study in SAB of the benefit of TTE vs TEE or the need to perform echocardiogram on all patients, irrespective of the computed risk or the pretest probability of IE. In a large prospective observational study of 724 patients with SAB, the strongest predictor of complicated SAB was a positive blood culture at 48–96 h after treatment [135]. Several studies have identified criteria for patients with lower risk of IE that might not require echocardiography, these include healthcare-associated or nosocomial SAB from central line, absence of intra-cardiac prosthetic devices, absence of clinical signs of IE, and documented brief bacteremia [<48–72 h] [136, 137]. In a recent retrospective study of 678 cases of SAB with 13% confirmed IE, a two-stage algorithm was proposed for optimal use of TEE based on the results from the Mayo Clinic [138]. On day 1 of admission patients with high risk of IE should undergo TEE, community acquired SAB with intracardiac prosthesis, or healthcare-associated SAB with CIED [cardiovascular implantable electronic devises] and presumably clinical signs of IE, repeat TEE later if no IE found and prolonged bacteremia present; day 5 second stage, perform TEE for community-onset SAB or intra-cardiac prosthesis [with nosocomial bacteremia] or prolonged bacteremia >72 h. In this algorithm, patients with healthcare-associated/nosocomial SAB without intra-cardiac prosthesis and bacteremia <72 h [and presumably transient bacteremia from skin/soft tissue infection] would not

require TEE, unless later signs of IE develop [138]. Five previous studies proposed that TEE could be avoided in low-risk patient for IE and the negative predictive values for the low-risk criteria were 93–100% [139]. In a multicenter retrospective cohort of 833 patients with SAB 536 underwent TTE within 28 days, and normal TTE ruled out IE in low-risk patients with a negative predictive value of 99% in a population with 14.2% IE prevalence [140].

Guidelines recommend that 2 weeks parenteral antibiotics can be used for uncomplicated SAB, but there is no randomized trial or large prospective study to assess the true efficacy. An earlier meta-analysis of short-course therapy for catheter-related SAB was inconclusive based on inadequate data [141]. The treatment duration of uncomplicated SAB was assessed in prospective observational cohort of 483 patients with SAB, 111 met the criteria for uncomplicated bacteremia [47.7% with MRSA] [142]. Comparison of short-course therapy <14 days [median duration 8.5 days] compared to longer-course therapy >14 days [median duration 16 days] showed no difference in treatment failure rates and crude mortality, but the relapse rate was higher in the those treated <14 days [3/38 or 7.9% vs 0/73]. Thus, short course of therapy of 7–11 days was associated with relapse in almost 8% of patients with SAB but 14–16 days prevented relapse.

10.4.3 Viewpoint on S. aureus *Bacteremia Management*

There is a need for good data on the management approach of SAB by randomized controlled trials and even large prospective observational studies with propensity-analysis matching of cases. The lumping of all patients with ≥1 blood culture positive for SAB used by guidelines is not very useful clinically to make decisions on embarking on expensive investigations and expose patients to unnecessary prolonged antibiotics. It is clear from many years of extensive clinical data that the patients with or at risk of IE and intravascular infections are those with continuous bacteremia with ≥2 positive blood cultures taken at least two hours and preferably two hours apart and associated with higher bacterial load, which may be detected by growth within 14 h of incubation [143]. Thus, patients with transient bacteremia [1 of ≥2 blood cultures] from skin/soft tissue or wound infections without intra-cardiac devises or previous IE should be managed as soft tissue infection [5–10 days antibiotics] without need for echocardiography.

Patients with uncomplicated SAB [at least two positive blood cultures taken at separate times] need not undergo TEE unless TTE is suspicious or there is significant cardiac valve abnormality. While TEE is more sensitive in detecting vegetations [85–90%] compared to TTE [75%], nearly all patients with IE have some valve abnormality which can be detected by TTE [144]. A randomized trial is warranted in low-risk patients with uncomplicated SAB to compare performance of TTE at 5–7 days after diagnosis, then TEE only for those with valve abnormality, versus no echocardiography unless indicated by clinical signs with follow-up after ≥6 weeks.

It is evident from the prospective study of treatment duration of uncomplicated SAB that >90% of patients treated with about 1 week of parenteral antibiotics will not have relapse of infection [142]. Therefore, a randomized controlled trial should be performed in patients with well-defined uncomplicated SAB to compare 7 versus 14 days of treatment. Presently a randomized trial of similar design is underway with estimated 284 participants to be completed by November 2021 [145]. Despite practice guidelines, there is substantial practice variation among adult infectious diseases physicians in the diagnostic evaluation and management of SAB which reinforces the need for proper randomized clinical trials [146].

Addendum Recently a new issue has arisen about the best treatment of MSSA bacteremia. For many decades the accepted standard therapy has been with an anti-staphylococcal penicillin. However, a recent large multicenter, retrospective study reported that cefazolin was more effective, with less adverse events than oxacillin or nafcillin [147]. A review of the data from several retrospective studies found no difference in outcome between cefazolin versus anti-staphylococcal penicillins [148]. But retrospective studies commonly have intrinsic flaws with biases that skew the results. Hence, a randomized trial to compare cfeazolin to cloxacillin in MSSA bacteremia is now in progress [149].

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Chapter 11
Issues and Concerns in the Management of Systemic Candidiasis

11.1 Introduction

Invasive candidiasis [IC] is an opportunistic infection with peak bimodal age distribution, premature neonates and the elderly, which is primarily nosocomial in origin or healthcare-associated from the community in patients with permanent or semi-permanent catheters for hemodialysis, intravenous fluids, or total parenteral nutrition [TPN]. Rarely, IC can result from transient candidemia from intravenous drug abuse [IVDA] in the community from injecting drugs contaminated with Candida species from the diluent. The epidemiology, incidence, and frequency of different species have been evolving over the decades. In the 1970s–1980s IC was most commonly associated with neutropenia from chemotherapy used in hematological malignancies, but since the advent of routine antifungal prophylaxis and empirical fungal therapy for febrile neutropenia this has become an uncommon cause of systemic candidiasis. IC is the most common systemic fungal infection worldwide with high mortality and morbidity associated with excessive hospitalization and healthcare costs.

11.2 Epidemiology

The global burden of IC has been difficult to assess as data are lacking from most developing and middle-income countries. Recent estimates largely from high- and middle-income countries suggest that ≈700,000 cases of IC occurs worldwide yearly, mainly from tertiary care centers [1]. The incidence of nosocomial candidiasis has been increasing in the past few decades in most reports except for declining incidence of candidemia reported from two United States [US] metropolitan areas in 2008–2013 [2]. Although the incidence of candidemia varies with geography

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regions, large national surveys reported incidence of 3–5 per 100,000 in the general population and 1–2% of all ICU admissions [3]. Candidemia is the most readily diagnosed form of IC and the prevalence varies by country, regions within the same country and medical centers. Intensive care units [ICU] accounts for 60% of candidemia cases followed by cancer and transplant units [13%] and 50% of the global burden were reported from Asia [78,778 cases], followed by the Americas [74,575 cases], Europe [42,549 cases], and Africa [19,602 cases] [1]. However, the data is incomplete as information from many countries are lacking from each continent. Candidemia is the most common form of IC and is associated with a combination of risk factors: central venous catheters, TPN, recent abdominal surgery, intra-abdominal infections, broad-spectrum antibiotics, multiple co-morbid illnesses [renal failure, diabetes, severe recurrent pancreatitis with abscess], and multiple sites of candida colonization [4]. Candidemia is the third or fourth most common cause of nosocomial blood stream infections in most developed countries and accounted for 18% of infections in a survey from ICUs around the world in 2009 [5].

IC without detectable candidemia and deep tissue invasion from transient blood stream invasion is more commonly associated with neutropenia and peritoneal inoculation with dissemination. IC is being increasingly recognized secondary to intra-abdominal candidiasis [Candida peritonitis or abscess] following rupture of the intestines and broad-spectrum antibiotics, and may account for up to 50% of the cases of IC in the ICU in some estimates. Prevalence data from 29 countries reported 17,640 cases of Candida peritonitis with an average incidence of 1.15 cases per 100,000 [1]. Occasionally, ascending renal infection can occur [especially in catheterized renal transplant patients] that lead to IC [4], but by large candiduria in the ICU is a benign condition that requires no specific therapy.

11.3 Pathogenesis of Invasive Candidiasis

Systemic candidiasis is a product of advance in medical technology and cancer therapy, as healthy people do not suffer from IC. While lymphocyte dysfunction from corticosteroids and human immunodeficiency syndrome [HIV] is associated with mucosal disease, not candidemia or IC, neutropenia is well established as a risk factor for disseminated candidiasis. However, in recent decades IC is associated with neutropenia in <20% of the cases [6]. Most patients [>80%] with IC are not immunosuppressed or neutropenic, but instead have break in the anatomic barrier with direct inoculation in the blood stream from central catheters and heavy colonization of candida from suppression of normal flora by broad-spectrum antibiotics, or direct inoculation into sterile sites as the peritoneum.

Whereas, T cells and their secreted cytokine Il-17 have protective role in mucosal candidiasis, the majority of studies have shown that the innate immunity mediated by myeloid derived phagocytes [neutrophils, macrophages, monocytes, and dendritic cells] provides the major defense for disseminated infection. In the murine model depletion of neutrophils and tissue macrophages were insufficient to induce

disseminated candidiasis, but required both mucosal damage [with translocation] and neutropenia for Candida dissemination [7]. Neutrophils are critical in the clearance of invading Candida species in the first 24–48 h [aided by mononuclear phagocytes] through complex signaling pathways that mediate production of inflammatory cytokines and chemokines that promote recruitment, phagocytosis, activation of myeloperoxidase and killing by reactive oxygen species, neutrophil extracellular traps [NETs], release of granule enzymes and antimicrobial peptides [8, 9]. Candida has evolved mechanisms to evade antimicrobial activity of local and circulating phagocytes by inhibiting recognition, trafficking, and effector release [9]. While phagocytes can efficiently ingest yeast cells, an evasion strategy is to form hyphae that cannot be phagocytosed and even when ingested can inhibit phagosome maturation.

The pathogenesis of IC in ICU patients is more complex and involves more than the inoculation of Candida species in the blood stream via catheters or the peritoneal cavity from ruptured bowel. In murine models monomicrobial inoculation of Candida does not result in disseminated disease but polymicrobial inoculation with bacteria is required to establish the model of IC [10]. A major predisposition for IC in the critical care is prior or multiple episodes of sepsis with multiple courses of broad-spectrum antibiotics that lead to Candida overgrowth with multiple sites of colonization. It is now evident from many studies that sepsis even after adequate treatment results in a state of prolonged inflammation with innate immune dysregulation and adaptive immune suppression [11]. Neutrophils and mononuclear phagocytes have functional deficiencies that persist after sepsis symptoms disappear that predispose to IC.

Candida utilizes several mechanisms to aid invasion and evade the host immune response such as phenotypic switching to hyphae, secretion of aspartyl proteinases [SAPs] and phospholipases to invade tissue [12]. SAPs have also been used as a maker of invasive disease.

11.4 Genetic Predisposition of Invasive Candidiasis

How can we explain the fact that most patients in the ICU with similar multiple risk factors do not develop IC and the wide variability in reported mortality [15–70%]? Genetic variability in key immune related genes appears to explain this enigma. Increased susceptibility to invasive candidiasis have been shown in population studies in humans with selected genetic variants including IL10, IL12B, TNF, CXCR1, STST1, PSMB8, SP110, CCL∗, TLR1, CD58, TAGAP, and LCE4A-C1orf68 [13]. Increased risk for candidemia was found in cohorts of ICU patients in Europe and North America associated with 3 single-nucleotide polymorphisms [SNPs] in the toll-like receptor 1-interferon-¥ pathway [14]. Patients carrying two or more alleles of three novel candidemia risk factors [CD58, TAGAP, and the LCEA-C1orf68 locus], variants known to be associated with immune-mediated diseases, were found in a genome-wide association study to have >19-fold increased risk of candidemia

[15]. Further studies revealed that CD58 may regulate Candida phagocytosis and indirectly IL-6 and TNF-α secretion, and SNP of this gene was also associated with persistent fungemia. TAGAP was found to have a role in Candida-induced inflammation and antifungal host defense, whereas LCE4-A-C1orf68 locus is involved anti-Candida barrier function at the epithelium [15]. Polymorphisms of genes that lead to increased anti-inflammatory interleukin [IL]-10 or decreased levels of pro-inflammatory IL-12b cytokine are associated with persistent candidemia and disease progression on antifungal therapy [16].

11.5 Microbiological Aspects

Candida species are part of the normal human flora that can be found colonizing the mouth, stool, and vagina [less commonly the skin] in 30–40% of healthy humans, with *Candida albicans* being the most prevalent. There are 150 Candida species of which 15 have been associated with human infections and the five most common causes of IC [95%] are *C. albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei* [17]. Over the past few decades the incidence of *C. albicans* invasive disease has decreased while non-*albicans Candida* has increased. International surveys have found that *C. albicans* has declined from 70 to 50% in invasive fungal infections [18]. In North America and many European countries the decreased *C. albicans* infections is replaced by increased *C. glabrata*, but other regions have reported increased incidence of *C. tropicalis* and *C. parapsilosis*. In Latin American countries *C. albicans* still remain the most common species isolated with low rates of *C. glabrata* and increased incidence of *C. parapsilosis* followed by *C. tropicalis* [17]. *C. parapsilosis* has a predilection for skin colonization and is most commonly associated with neonatal IC and venous catheters in ICUs. Increased frequency of *C. parapsilosis* infection is also reported from Australia, southern Europe and some Asian countries, and risk factors include younger age, inadequate infection control practices and exposure to echinocandins [17]. Whereas, in general the shift to non-*albicans Candida* species in many countries is associated with frequent prophylactic and therapeutic use of fluconazole. *C. glabrata* which has intrinsically reduced susceptibility to fluconazole is increasingly found in the elderly in northern Europe and North America and may be responsible for up to 30% of candidemia [19]. The virulence of Candida species differ in animal models with *C albicans* and *C. tropicalis* being the most virulent, followed by *C. glabrata*, *C. kefyr,* and *C. lusitaniae*, then *C. parapsilosis*, *C. krusei,* and *C. guilliermondii* among the eight strains tested [20].

Of major concern is *Candida auris* which is a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infection worldwide. *C. auris* was first isolated from the external ear canal of a patient in Japan in 2009 and after a decade it has been reported in over 30 countries on six continents [21]. *C. auris* was previously misidentified as *Candida haemulonii* and the earliest confirmed isolate [retrospectively] was from blood culture of a patient in South Korea in 1996 [22]. *C. auris*,

based on the geography location of the initial isolate, has been divided into four clades: South Asian [clade I], East Asian, the original isolates [clade II], African [clade III], and South American [clade IV] [21]. Clade II has the unusual propensity for the ear and >93% of 61 isolates was from ear infection [23]. Other clades are rarely recovered from the ear but can colonize skin and other body sites indefinitely, persist on healthcare environmental surfaces and equipment, allowing transmission between patients [24]. Similar to multi-resistant bacteria, *C. auris* can cause intra- and inter-hospital or healthcare-associated transmission with outbreaks of invasive disease, thus colonized patients are of major infection control concern. This is unlike other Candida species, except for occasional *C. parapsilosis* nosocomial transmission, which are acquired from endogenous source or autoinfection. The main concerns of *C. auris* are the rapid global emergence, multidrug resistance is common and a few isolates are resistant to all three classes of antifungal agents, misidentification is common in clinical laboratories, and the ability for nosocomial transmission between patients and cause outbreaks. *C. auris* has caused healthcare outbreaks in India, Colombia, Pakistan, Panama, Spain, the United Kingdom, the US and Venezuela and is now the leading cause of candidemia in South Africa and some centers in India [25]. Strict isolation precautions are recommended for infected or colonized patients, similar to those with methicillin resistant *Staphylococcus aureus* [MRSA] [25].

C. auris differs from other Candida species with its ability to grow at high temperatures up to 42 °C and high salt concentration and seldom form rudimentary pseudohyphae [25]. It is frequently misidentified by different biochemical systems used in laboratories and the most reliable methods include the MALDI-TOF MS system, and possibly others such as Quest Diagnostic's CMdb, CDC's MicrobeNet and VITEK 2 with 8.01 software update [25]. Several commonly used hospital disinfectants are not effective against *C. auris*, but chlorine detergents [sodium hypochlorite] and hydrogen peroxide are effective disinfectants, and ultraviolet light for room decontamination does not appear to be effective [26].

The pathogenic mechanisms and virulence of Candida species have been studied in *C. albicans* and these include molecules which mediate adhesions to and invasion of host cells, the secretion of enzymes [hydrolases], the yeast-to-hyphae phenotypic switching, contact sensing, biofilm formation, and other survival methods [27]. *C. auris* also form biofilm [less robust than *C. albicans*], form aggregates on culture, and have similar virulence factors. In animal models, *C. auris* demonstrated similar or slightly less virulence than *C. albicans* and *C. tropicalis* [28]. Table 11.1 shows the relative proportion of Candida species isolated in IC.

11.6 Clinical Aspects of Invasive Candidiasis

The clinical manifestations of IC varies widely from fever without specific signs to presentation with septic shock or sepsis syndrome, the latter most commonly in critically ill patients with polymicrobial infection. Nonspecific fever with candidemia

Table 11.1 Distribution of Candida species causing candidemia and usual susceptibility pattern

Species	Proportion	Fluconazole	Echinocandin	Comments
C. albicans	38–62%	S	S	Rates varies with country, but declining
C. tropicalis	10–26%	S	S	Increasing in some centers
C. parapsilosis	17–38%	S	S/I	Higher in Latin America
C. glabrata	5–29%	I	S	Higher in Europe/N. America
C. krusei	1.8–7.9%	R	S	Mainly in cancer/immunosuppressed
C. auris	Emerging	R	S	7% Ech. R, 45% R to 2, 4% R to 3 classes

Ech. echinocandin, *I* intermediate or susceptible to high dose [S-DD], *R* resistant, *S* susceptible, *R to 2* resistant to two antifungal classes [azole and amphotericin], *R to 3* resistant to all three antifungal classes

is the most commonly recognized entity and candidemia with deep organ involvement [eye, skin, muscle, bone, joint, central nervous system, kidney, heart valve, lung, liver, and spleen] are now infrequent due to early treatment. Deep organ invasion or sepsis without candidemia is more commonly seen in severe neutropenia and increasing recognized in patients with severe necrotizing pancreatitis and recurrent intestinal leaks treated with repeated courses of broad-spectrum antibiotics [29–31]. Primary candida peritonitis is a moderately severe disease that is easily treated and seen in patients on chronic peritoneal dialysis. Secondary candida peritonitis and Candida abscess have been increasingly recognized in ICU patients with nosocomial intestinal perforations and refractory necrotizing pancreatitis. *C. auris* invasive disease is similar to other Candida species and is most commonly associated with candidemia, but can be found in other body sites from dissemination or intra-abdominal fluids [25].

The attributable mortality from IC is difficult to assess as reported rates from various studies varied markedly from 5 to 70%. The mortality rate has not declined significantly since echinocandins have become first-line therapy in many centers globally and ranges from 40 to 60% at 30 days after diagnosis of candidemia [32]. In general the mortality rate is higher in patients from the ICU and those with hematological malignancy, a reflection of the severity of disease with comorbid conditions. *C. auris* candidemia mortality rates are similar, from 30 to 60% depending on the setting [25].

11.7 Diagnosis of Invasive Candidiasis

The diagnosis of IC can be difficult and delayed depending on the source and underlying mechanism of the disease. Although, it is commonly quoted that blood cultures are positive for Candida species in only 38% [range of 21–71%] of IC based on autopsy studies [33], this is misleading as nearly all the data were obtained from patients with hematological malignancies [usually with severe neutropenia] and

those with candidemia but no organ involvement at autopsy were excluded. Thus, the sensitivity of blood cultures for candidemia at some point is closer to 63–83% [33]. In localized intra-abdominal candidiasis [abscess, peritonitis, infected pancreatic necrosis, and biliary tract infection] candidemia has been reported in only 6–14% [34, 35]. Overall, it is estimated that blood cultures will detect only 50% of patients with IC including those with candidemia and deep-seated candidiasis without candidemia [33]. The concentration of Candida cells in patients with candidemia is usually <1 colony forming units [CFU]/mL [36], thus larger volumes of blood cultured would be more sensitivity in detecting candidemia. IC in the ICU is most commonly due to central line infection and candidemia may best be detected by culturing blood from the central lines, where the concentration of yeast is highest, as well as peripheral blood. The disadvantage of blood cultures is the delay in obtaining results, which usually takes 2–3 days, and prompt specific antifungal therapy may make a difference in the outcome.

The concern of missing the diagnosis of IC in neutropenia patients on cancer therapy is less of a concern in recent decades, due to the standard practice of adding antifungal therapy for patients with febrile neutropenia after 3–5 days of persistent fever on broad-spectrum antibiotics. The present diagnostic dilemma is mainly for patients with recurrent fever after courses of antibiotics in subjects with necrotizing pancreatitis or bowel perforation. In this scenario it is preferably to obtain percutaneous aseptic aspiration of fluid collection or necrotic tissue for bacterial and fungal cultures [not from drainage catheters] based on imaging findings. However, in some cases this may not be feasible due to inaccessible collections. The isolation of Candida from the peritoneal fluid does not reflect Candida peritonitis or IC and antifungals are not necessary in community acquired peritonitis from ruptured intestines [37]. This is in contrast with recurrent peritonitis or abscess after previous abdominal surgery where IC is a greater risk and early empirical antifungal may be of benefit. Candida species have been isolated from intra-abdominal specimens in 24.6% of community acquired peritonitis [n = 166] and 20.9% of post-operative peritonitis [n = 224] in a large cohort of intestinal perforations or leaks from anastomosis [38]. However, the clinical significance of Candida isolation from the peritoneum is controversial, as in most patients it does not cause disease [>60%], but more likely to cause infection [abscess or peritonitis] in patients with pancreatitis having surgery than those with intestinal perforation [39].

In the past decade several studies have assessed the value of non-culture methods for the rapid diagnosis of IC. These include serum assays for Candida antigen and antibodies [mannan/antimannan], *C. albicans* germ-tube antibody [CAGTA], 1,3-β-D-glucan [BDG] antigen, PCR and the T2Candida nanodiagnostic panel. Most of these tests have not been approved by the US Food and drug Administration [FDA] except for the T2Candida panel. The serological/antigen assays have low sensitivity 25–73% and moderate specificity of 54–83%, greater for antigen assays; and PCR have better sensitivity [86–91%] but low specificity [33–97%] [40]. The T2Candida panel uses T2 magnetic resonance and a special dedicated instrument to detect Candida DNA in whole blood. FDA approval of T2Candida was based on results of the DIRECT trial, which included 6 patients with candidemia by blood

cultures, 250 spiked blood samples with *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* with concentrations of 1–100 CFU/mL and >1500 control patients with negative fungal blood cultures [41]. The sensitivity and specificity were estimated to be 91% and 98%, respectively, for detecting candidemia. In a follow-up, multicenter DIRECT2 trial 152 patients with recent positive Candida blood cultures [1–6 days] had repeat blood cultures and T2Candida test, mean of 55.5 h after diagnosis [42]. T2Candida was significantly more likely to remain positive than blood culture [45% versus 24%], mainly from prior antifungal therapy. The benefits of the T2Candida test include the reduction in time for detection of candidemia from 3–5 days to few hours and the ability to detect Candida after empirical antifungals. The limitations are lack of species identification and susceptibility, and the inability to detect other Candida species other than the five commonest causes of candidemia, thus would not detect *C. auris*. The T2Candida is for the rapid diagnosis of candidemia and not likely to improve the diagnosis in intra-abdominal candidiasis. Overall, the non-culture diagnostic tests have low positive predictive value and high negative predictive value in most settings [40]. For instance, a recent study of ICU patients with suspected IC with severe abdominal conditions found serological tests [CAGTA and BDG] in combination from one sample or singly from two consecutive samples of blood were 90.3% sensitive and 42.1% specificity, with 96.6% negative predictive value [43]. However, the T2Candida panel may be useful for identifying patients with complicated candidemia who need longer course of antifungals. In a recent prospective study of patients with candidemia repeat blood tests within the first 5 days of diagnosis, T2Candida was more effective than blood culture and BDG in predicting patients with complicated candidemia [risk of dying and metastatic infection] [44].

11.8 Resistant Patterns of Candida Species in Invasive Disease

The resistance pattern of Candida species has been best studied with fluconazole and the echinocandins with revised breakpoints by the Clinical Laboratory Standards Institute [CLSI] [45]. The major changes from previous standards are that the new breakpoints are now both drug and species specific for most species, with the exception of *C. parapsilosis* and *C. guilliermondii* against the echinocandins; the breakpoints have been lowered with previous susceptible MICs breakpoints now classified as resistant [46]. *C. glabrata* is no longer considered fluconazole susceptible but is either dose-dependent susceptible [S-DD] [MIC ≤32 μg/mL] or resistant. Isolates of Candida species that are designated S-DD may respond to higher doses of fluconazole ≥400 mg daily. Resistance of Candida species can be intrinsic or acquired resistance from previous drug exposure, and most trends in increased resistance is due to increasing prevalence of species with intrinsic resistance, i.e. *C. glabrata* and *C. auris* [19]. See Table 11.1 for usual susceptibility patterns.

In North America [US data], fluconazole resistance is rare [≤3%] in candidemic isolates of *C. albicans*, *C. tropicalis* and *C. parapsilosis*, but much higher [18%] for

C. glabrata, based on data before 2010 [47]. Data from the SENTRY Antimicrobial Surveillance Program with 3107 isolates of 21 Candida species from 34 countries collected from 2010–2011, using the new CLSI breakpoints reported low fluconazole resistance among isolates of *C. albicans* [0.4%], *C. tropicalis* [1.3%], and *C. parapsilosis* [2.1%]; but 8.8% of *C. glabrata* were resistant to fluconazole [48]. All isolates of *C. krusei* were intrinsically resistant to fluconazole. Resistance to echinocandins was low [0.0–1.7%] among the Candida species, except *C. parapsilosis* is intrinsically more resistant with higher MICs [19]. *C. glabrata* isolates are intrinsically relatively resistant to fluconazole due to efflux pumps, but previous fluconazole use increases the risk of resistant strains [49]. Azole resistant *C. glabrata* is associated with mutation in the transcription-factor PDR1 gene, whereas azole resistance to *C. albicans*, *C. tropicalis* and *C. parapsilosis* is mainly due to mutations in the ergosterol biosynthesis gene, especially ERG11 [50]. There is also evidence that echinocandin resistance in *C. glabrata* is increasing in some US centers, from 4.9 to 12.3% in one major center between 2001 to 2010 [51]. Echinocandin resistance is mainly mediated by mutations in Candida FKS genes, which encode β-1,3-D-glucan synthase, the enzyme targeted by echinocandins, and FKS mutation is associated with treatment failure of >50% [51–53]. Prior echinocandin exposure is associated with 20-fold increased risk of isolating a FKS resistant mutant [51, 52] and 30% of isolates may carry the mutation [53]. However, among 1385 *C. glabrata* isolates collected across the US during 2008–2014, 83 [6%] were nonsusceptible to echinocandins [19 intermediate and 64 resistant], an increasing trend from 4.2% in 2008 to 7.8% in 2014 [54]. Although previous exposures to echinocandin and fluconazole resistance were risk factors for recovery of nonsusceptible strains, 59% of the cases had no known exposure.

A study of antifungal susceptibility of Candida bloodstream isolates collected from patients in 2012–2014 in 13 centers of the Asia-Pacific region was recently reported [55]. Non-*albicans* species exceeded *C. albicans* isolates in all countries except Taiwan with the following distribution: *C. albicans* [30.7%], *C. tropicalis* [30.7%], *C. parapsilosis* [15.7%], and *C. glabrata* [13.6%]. Fluconazole susceptibility was as follows: *C. albicans* [S = 99.7%], *C. tropi*calis [S = 75.8%, S-DD = 6.1%], *C. parapsilosis* [S = 94.8%], and *C. glabrata* [S-DD = 94.9%]. Echinocandin resistance remained low for all isolates in this study and reduced susceptibility was most evident for *C. glabrata*. International data over 20 years showed the highest rates of fluconazole resistance were seen in *C. glabrata* from North America [US] [10.6%] and in *C. tropicalis* from the Asia-Pacific region [9.2%] [56].

Most recently the Ontario Public Health Laboratory, a Canadian reference laboratory, performed in vitro susceptibility on 3386 Candida species of which 74% were from sterile sites. In 2029 *C. albicans* isolates, 98% were susceptible to fluconazole and 100% to echinocandins; among 994 C. *glabrata* isolates, 91% were fluconazole susceptible [S-DD] but 45% highly susceptible, and 93-99% were echinocandins susceptible; in 708 *C. parapsilosis* isolates, 83% were fluconazole susceptible [previously 90% in 204] and 100% were echinocandin susceptible; and among 294 *C. tropicalis* isolates, 79% were fluconazole susceptible and 100% echinocandin susceptible [unpublished, personal communication with Julianne Kus].

C. auris is intrinsically resistant o fluconazole and occasionally multiresistant to all three classes of antifungal agents. Susceptibility testing of 350 isolates collected

in India over 8-year period showed that 90% were resistant to fluconazole, 2% to echinocandins, 8% to amphotericin B and 2.3% to voriconazole [57]. Resistance to the azole was mediated by mutations to ERG11 gene and to echinocandins by mutations of the FKS1 gene. In the US, *C. auris* isolates were resistant to fluconazole in 90%, to amphotericin B in 30%, and to the echinocandins in 5%, but 10% of isolates in the United Kingdom [UK] were echinocandin resistant [25]. In a recent study *C. auris* biofilms did not show susceptibility to any antifungals and the minimal biofilm eradication concentrations [MBECs] were up to 512-fold higher than the MICs [58]. For biofilms of *C. albicans* and *C. parapsilosis* the MBECs for the azoles and echinocandins also markedly increased, but maintained susceptibility to amphotericin B.

11.9 Management of Invasive Candidiasis

The management issues of IC that will be addressed are mainly for non-neutropenic patients primarily found in the ICUs with confirmed diagnosis [most commonly candidemia] and the evidence for empiric treatment for suspected abdominal candidiasis.

In patients diagnosed with IC prompt treatment should be instituted consisting of source control, removal of infected central catheters or drainage of candida abscess, and employing specific antifungal agents. In the past several years, the choice of initial antifungal agent for treatment of IC has changed in most centers and guidelines from fluconazole to an echinocandin [caspofungin, micafungin, or anidulafungin]. In 2016, the Infectious Diseases Society of America [IDSA] updated guidelines for management of IC, recommended initial echinocandin agent for most patients with candidemia, but considered fluconazole as suitable initial therapy in clinically stable patients without previous azole exposure [59]. Clinically stable patients initially started on an echinocandin could be switched to fluconazole for fluconazole-susceptible isolates. The guidelines are also applicable to the candidemic neutropenic patients [59]. In general uncomplicated candidemia or IC is treated for 2 weeks and those with metastatic infection for 4–6 weeks, but the optimal duration has not been assessed by prospective studies.

There are several advantages of fluconazole compared to an echinocandin besides being less expensive, see Table 11.2 for cost per dose. Fluconazole oral bioavailability is >90% and it can be administered orally or intravenously [IV], once intestinal absorption can be assured. It is widely distributed in the body with cerebrospinal fluid [CSF] and aqueous/vitreous concentrations above 60–70% of serum concentrations and it is eliminated unchanged in the urine [60]. The echinocandins are not available orally and they achieve poor concentrations in the CSF, aqueous/vitreous humor and urine [<5%, <1%, <2%, respectively, of serum concentration] [60]. Hence, echinocandins should not be used for IC of the meninges and eyes or possible candida urosepsis.

The echinocandins activity [in vitro and in animal models] is fungicidal and more potent than fluconazole [61]. Although fluconazole is a fungistatic agent, it is similarly effective as the rapidly fungicidal amphotericin B in nonneutropenic

Table 11.2 Relative costs of fluconazole compared to echinocandins

Drug	Route/formulation	Dosage (mg)	US-cost	Canada-cost
Fluconazole	IV/piggyback	200	$ 10.68–18.68	$ 8.23
		400	$ 15.13–21.82	$ 21.34
	PO/tablet	200	$ 13.60–44.0	$ 4.29
Micafungin	IV/vial	50	$ 122.0	$ 41.51
		100	$ 224.40	$ 83.0
Caspofungin	IV/vial	50	$ 405.25	$ 75.0
		70	$ 421.06	$ 90.0
Anidulafungin	IV/vial	50	$ 108.00	N/A
		100	$ 216.00	N/A

Reference: For US costs only—John Hopkins ABX Guide; https://www.hopkinsguides.com/hopkins/view
N/A not available, *PO* oral, *IV* intravenous

patients with candidemia [62]. Only one randomized controlled trial compared fluconazole to an echinocandin [anidulafungin] in patients with IC, 89% with candidemia, treated for at least 2 weeks [63]. Successful outcome was achieved in 71/118 [75.6%] patients treated with anidulafungin, as compared to 71/118 [60.2%] in the fluconazole group at the end of intravenous therapy [95% confidence interval [CI], 3.9–27.0; $p = 0.01$]. However, exclusion of data from the highest enrolling center with exaggerated treatment-response revealed non-significant statistical difference in response, 73.2% and 61.1%, CI = −1.1 to 25.3. At 6 weeks follow-up the successful response appeared greater in the anidulafungin group than the fluconazole group, but not significantly greater and the mortality was not significantly lower, 23% vs 31%, $p = 0.13$ [63].

A patient-level review of seven randomized trials from 1989 to 2006 of 1915 patients with IC [85% with candidemia] was analyzed and reported by the Mycoses Study Group in 2012 [64]. Predictors of mortality were increasing age, Acute Physiology and Chronic Health Evaluation II score, immunosuppressive therapy and *C. tropicalis*, but removal of central venous catheters and echinocandin antifungals were associated with decreased mortality. Patients treated with an echinocandin was reported to have better survival than those given amphotericin formulation or azole, with mortality rates of 27%, 35%, and 36%, respectively, $p = 0.0001$ for echinocandin vs others. However, three trials included in the analysis did not include echinocandin in the treatment arm. When only those trials that compared an echinocandin to another agent were pooled for analysis, no significant difference in mortality exists, 23% vs 24% for comparators [60]. In a prospective, multicenter, observational study in Spain [168 epidsodes of candidemia] the overall mortality at 30 days remained high [47%] despite type of treatment and outcome was mainly related to host factors [65]. Similarly, analysis of the AmarCAND2 study of 397 patients showed no survival benefit of echinocandins over azole at 28 days [66]. In the CANDIPOP study, a multicenter prospective, population-based cohort study in Spain, using propensity scoring to compare the 30 day mortality for empirical [$n = 316$], before susceptibility, and targeted [$N = 421$] therapy, after susceptibility, with fluconazole or echinocandins [67]. The 30-day mortality in the empirical

therapy group was 18.7% with fluconazole and 33.9% with echinocandins [$p = 0.02$]; and for targeted therapy group 19.8% with fluconazole and 27.7% with echinocandins [$p = 0.06$]. The results were similar for patients with severe sepsis or septic shock. A smaller prospective study of 130 candidemic patients not admitted to ICU showed similar findings, that clinical severity but not the initial antifungal strategy correlated with mortality [68]. In a large, retrospective multicenter study, patients with abdominal candidiasis [$n = 481$, 14% with candidemia], 64% treated with echinocandins and 32% with azoles, outcome or mortality was not related to specific therapy but to the severity of illness [septic shock, secondary peritonitis], age, physiological score and absence of adequate source control [35]. In patients with septic shock mortality was >60% irrespective of adequate antifungal therapy in the absence of source control. See Table 11.3 for comparative results of fluconazole and echinocandin in IC.

Is there evidence that empirical antifungal therapy for suspected IC reduces mortality in the ICU? The IDSA guidelines for management of candidiasis recommended consideration of empiric antifungal treatment for high risk patients with clinical signs of sepsis [59]. A multicenter double-blind placebo-controlled trial of 260 nonneutropenic critically ill patients with ICU-acquired sepsis, multiple Candida colonization, multiple organ failure, exposed to broad-spectrum antibiotics were randomized to empiric micafungin or placebo in French ICUs [69]. At 28 days survival and freedom of invasive fungal infection in the two groups were not significantly different, 68% with antifungal vs 60.2% for placebo.

Another related but separate issue is the effect of preemptive or prophylactic antifungal in prevention of IC. In a randomized controlled trial of ICU patients following intestinal surgery for intra-abdominal infection, 124 patients received placebo and 117 patients received micafungin for preemptive therapy to prevent IC

Table 11.3 Prospective studies comparing echinocandin to fluconazole in invasive candidiasis

Study type	Patient nos.	Candidemia rate	Outcome/mortality [≥28 days]	Comments	Ref.
1. RCT	236	89%	NS /31% F v 23% E [$p = 0.13$]	E faster response	[62]
2. Observ. [AmarCAND2]	397	38.5%	NS	E + trend in septic shock	[65]
3. Oberv. [CANDIPOP]	164	100% [$n = 168$]	47%	Outcome not related to Rx	[64]
4. Observ. [CANDIPOP]	316 [empirical]	100%	F = 18.7%, E = 33.9%	$p = 0.02$	[66]
	421 [targeted]	100%	F = 19.8%, E = 27.7%	$p = 0.06$	
5. Observ. [non-ICU]	130	100%	30.8%	Outcome not related to Rx	[67]

In no. 4 empirical group initiated antifungal before susceptibility; targeted group initiated antifungal based on susceptibility

E echinocandin, *F* fluconazole, *NS* not significant, *Observ.* observational, *RCT* randomized controlled trial, *Rx* treatment

[70]. However, the incidence of IC was 8.9% for placebo and 11.1% for micafungin, not significantly different. These results are similar to another randomized trial of preemptive caspofungin in high risk ICU patients [$n = 222$] [71]. It should be noted that exposures to antifungals are associated with increased resistance, which is a negative effect of empiric and preemptive antifungal therapy. In a study of 193 episodes of candidemia, post-treatment antifungal resistance was common in *C. glabrata* reservoir, with acquired resistance to fluconazole [29.4%] and anidulafungin [21.6%] [72].

11.9.1 Conclusion and Comments

The present therapeutic data does not prove that echinocandins are superior to fluconazole in treatment of IC with respect to final outcome. Anidulafungin appears to clear candidemia faster with quicker response to treatment but the survival at 6 weeks is not better than with fluconazole [73]. One of the arguments being touted for initial echinocandin therapy for IC is the increased reports of relatively fluconazole-resistant Candida species [i.e. *C. glabrata*] from epidemiological studies. However, in an analysis of *C. glabrata* blood stream infection [$n = 94$] initial fluconazole therapy was not associated with poorer outcome than that with echinocandins/amphotericin formulations [74]. Moreover, in a recent study of 257 episodes of candidemia high fluconazole MIC values did not negatively impact outcome of patients treated with fluconazole [75]. Certainly based on in vitro data, IC due to proven or suspected *C. auris* should be treated with an echinocandin.

Further research and studies are needed to improve the rapid diagnosis of IC with highly sensitive and specific methods, and to develop novel means or drugs to improve the overall longer-term survival of patients with IC. Overuse of antifungals, similar to antibiotics, appears to be driving the shift from sensitive strains of Candida species to more intrinsically resistant strains. This trend of empiric and preemptive antifungal therapy in ICUs may be partly responsible for the emergence of the potentially multiresistant *C. auris*, which is readily transmitted between patients and is of public health concern.

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Chapter 12
Emerging and Difficult to Treat Nontuberculous Mycobacteria Infections

12.1 Introduction

Nontuberculous mycobacteria [NTM] are a diverse group of bacteria found in the environment in water and soil globally and only a few of the 169 known species have been linked to human diseases. They are slow-growing bacteria with the ability to form biofilms, resist high temperatures, and grow in environments with low nutrient and oxygen content, but cell surface hydrophobicity is the major factor sustaining NTM in the biofilms of natural waters, drinking water distribution systems, hospitals, and household plumbing [1]. NTM are found in aerosolized particles present above natural bodies of water, hot tubs, spas, showerheads, humidifiers, and biofilm that form in these sites [2]. The NTM species most commonly recovered from various bodies of water, including water distribution systems, soil, and dust include *Mycobacterium avium, Mycobacterium chelonae, Mycobacterium gordonae, Mycobacterium kansasii,* and *Mycobacterium xenopi* [1, 2]. Increased risk of NTM infection in susceptible hosts is associated with environmental factors such as high humidity and high evapotranspiration [movement of water from land to the atmosphere] [3]. It is likely that most patients acquire their infection from repeated exposures to environments with bioaerosols enriched with NTM inhaled into the lungs [1]. However, small outbreaks of nosocomial NTM infection with novel species after surgical procedures have been reported. Occasionally some species cause skin and soft tissue infections from minor trauma with soil contamination in normal subjects.

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12.2 Microbiological Aspects

The family Mycobacteriaceae consists of a diverse group of bacteria with widely different traits in pathogenicity for humans and animals, reservoirs and growth dynamics in culture. They are aerobic, non-spore-forming, nonmotile Gram-positive, acid-fast bacilli with some species slightly curved or exhibit some branching and all contain mycolic acid in their cell wall [4]. NTM previous classification by the Runyon system based on their growth rates on solid medium and pigment formation [group I-IV] has largely been abandoned. Identification by growth characteristics and biochemical tests have been replaced by molecular methods, in-house or commercial systems, using DNA probes, PCR restriction analysis, or genetic sequencing of conserved genes [5]. In recent years the diagnostic laboratories are able to identify common, rapid growing NTM by the matrix-assisted laser desorption ionization-time of flight [MALDI-TOF] mass spectrometry.

NTM is classified based on growth rate on solid media [similar to the Runyon classification] into rapid growers [≤7 days] and slow growers [≥7 days], both groups can be widely found in the environment and only a few species have been associated with clinical disease [4]. The rapid growing NTM most commonly implicated in human diseases are: (1) *Mycobacterium abscessus* complex with three subspecies [*M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii,* and *M. Abscessus* subsp. *massiliense*]; (2) *M. chelonae* complex with four species [*M. chelonae*, *Mycobacterium franklinii, Mycobacterium immunogenum,* and *Mycobacterium salmoniphilum*]; and (3) *Mycobacterium fortuitum* complex with ten species: *M. fortuitum*, *Mycobacterium peregrinum*, *Mycobacterium senegalense*, *Mycobacterium setense, Mycobacterium septicum, Mycobacterium porcinum, Mycobacterium houstonense, Mycobacterium boenickei, Mycobacterium brisbanense,* and *Mycobacterium neworleansense* [4]. *M. abscessus* complex is most commonly associated with pulmonary infection in subjects with chronic lung disease, less commonly with skin, soft tissue, and bone infections following trauma and surgery or injection, and occasionally with disseminated infection in immunosuppression. *M. chelonae* complex most commonly cause infection of the skin, soft tissue, and bone after piercing wounds, tattoos, plastic surgery including liposuction, occasionally after ophthalmic surgery or contact lens wear, and rarely disseminated infection in the immunosuppressed. *M. fortuitum* is most frequently associated with skin, soft tissue, and bone infections resulting from trauma or surgery [mammoplasty, other plastic surgery, and cardiac surgery] and rarely pulmonary or disseminated infection in the immunocompromised host.

Slow growing NTM frequently involved in human disease include: (1) *M. avium* complex [MAC] with two species [*M. avium* and *Mycobacterium intracellulare*] and four subspecies of *M. avium* [*M. avium* subsp. *avium, M. avium* subsp. *hominin-issuis, M. avium* subsp. *paratuberculosis, M. avium silvaticum*], and numerous additional sequence variants within MAC [most notably *Mycobacterium chimaera*]; (2) *M. kansasii*; (3) *M. xenopi*; (4) *Mycobacterium malmoense*; (5) *Mycobacterium haemophilum*; (6) *Mycobacterium genavense*; (7) *Mycobacterium marinum*; (8)

Mycobacterium szulgai; and (9) *Mycobacterium scrofulaceum* [4]. A summary of the main NTM causing human disease is shown in Table 12.1.

12.3 Epidemiology of Nontuberculous Mycobacteria

Although NTM species are ubiquitous in the environment with worldwide distribution, NTM-associated diseases [predominantly pulmonary] are mainly reported from developed countries with very low rates of tuberculosis [TB] and rarely reported from developing countries with high rates of endemic TB. Thus, it is possible that TB exposure provides cross-reactive protection against NTM infection to explain this distribution. Epidemiology data on NTM is only on pulmonary infection, which is the commonest manifestation, based on sputum culture. The prevalence of NTM pulmonary infection since 2000 has continued to increase [population-based data] in North America, Europe, New Zealand, and Australia [6]. In North America and Australia the annual prevalence ranges from 3.2 to 9.8 per 100,000, higher than Europe where the estimates are <2 per 100,000. Studies from tertiary care centers from South Korea, Japan, and Taiwan suggested increasing prevalence of NTM pulmonary disease. A recent study from South Korea showed increased prevalence and incidence from 2007 to 2016, with annual prevalence of 39.6 cases per 100,000 in 2016 and annual incidence of 19.0 cases per 100,000 [7].

Table 12.1 Nontuberculous Mycobacteria causing disease

Organism	Disease
Rapid growers	
M. abscessus	Lung, disseminated, others
M. chelonae	Skin/soft tissue, disseminated
M. fortuitum	Skin/soft tissue, disseminated
M. marinum	Skin/soft tissue
M. mucogenicum	Catheter bacteremia
Slow growers	
M. avium complex	Lung, disseminated, lymph nodes
M. kansasii	Lung, lymph node
M. xenopi	Lung
M. simiae	Lung
M. scrofulaceum	Lymph node
M. szulgai	Lung
M. malmoense	Lymph node, lung
M. haemophilum	Lymph node, disseminated
M. genavense	Disseminated
M. ulcerans	Skin [Buruli ulcer]
M. terrae complex	Disseminated
M. chimaera	Cardiac implants, disseminated

In Japan the incidence of MAC infection increased from 5.2 per 100,000 in 2007 to 13.1 per 100,000 in 2014 [8]. In South America, Africa, and the Middle East, sputum cultures for investigation for suspected TB have reported NTM in 4–20% in various studies [6], but whether or not this represents NTM pulmonary disease or colonization is unclear. Although national data is lacking from China, in rural Shandong province only 64 of 2949 [1.6%] sputum specimens that grew mycobacteria were NTM [9]. In North America and East Asia MAC is the predominant NTM recovered, but in Europe *M. kansasii, M. xenopi,* and *M. malmoense* are more common [6].

12.4 Pathogenesis of Nontuberculous Mycobacteria Infection

NTMs are opportunistic pathogens that rarely cause disease in healthy humans unless introduced into normally sterile sites of the body by trauma, piercing injuries, injections, and a variety of surgical procedures and indwelling catheters. Immunosuppressive conditions and therapies may result in deep localized or disseminated infections, mainly as a result of impaired cellular immunity or T cell function. These include steroid use, immunomodulatory drugs, and biologics used in organ transplantation, rheumatic and autoimmune diseases, and cancers. Before the advent of highly active antiretroviral agents [ART], disseminated MAC was frequently found in patients with advanced acquired immunodeficiency syndrome [AIDS] in North America and Europe, but this is now rare due to early universal ART once the diagnosis of human immunodeficiency virus [HIV] infection is made. Reports of isolated or collection of patients with disseminated NTM with no recognized immunosuppression [10] likely represent subjects with undetected impaired cellular immunity such as defects in the interferon-¥ or interleukin-12 pathways which requires special investigation [11].

Pulmonary disease [PD] associated with NTM are in most cases due to underlying chronic lung disease with impaired local defense such as cystic fibrosis [CF], non-CF bronchiectasis, chronic obstructive pulmonary disease [COPD being the commonest], neoplasms of the larynx or lung, thoracic skeletal abnormalities, steroid or immunomodulatory drugs, rheumatoid arthritis, and possibly gastroesophageal reflux disease [6]. However, NTM-PD in elderly white women without any obvious risk factors was described since 1989 [12]. A prospective study with extensive investigation was performed by the National Institute of Health on a cohort of 63 patients with similar features [13]. Compared to match controls, the patients were taller and leaner with high rates of scoliosis, pectus excavatum, mitral valve prolapse, and CF transmembrane conductance regulator mutation, but no recognized immune defects. Symptoms started at a mean age of about 50 years and 95% were female and 91% white. The complex preexisting morphotype in a relative homogenous group of white women strongly suggest an underlying genetic mutation with possible unrecognized immune defect. The role of environmental factors

such as exposure to soil, land surface water, and coastal waters is unclear as studies have been inconsistent [6].

There are microbial factors that are important in the pathogenesis of NTM disease. Glycolipids [glycopeptidolipids, GPLs] that are components of the cell wall, produced by several pathogenic and nonpathogenic Mycobacterium species have been implicated in the pathogenesis of NTM diseases [14]. GPLs are produced by pathogenic rapid growing NTM [i.e., *M. abscessus* and *M. chelonae*] and slow growing NTM [i.e., *M. avium* and *M. intracellulare*] and have been shown to alter cellular functions through their interaction with host receptors mediating macrophage phagocytosis [14]. Studies with *M. avium* purified GPLs suggest that these glycolipids can modulate the innate and T cell immune responses and abrogate the proinflammatory response [14]. These pathogenic mycobacteria are intracellular pathogens that survive inside phagocytic cells by blocking the phagosome–lysosome, and GPLs appear to aid in the survival of MAC by disrupting the phagosome membrane or provide a protective barrier against lysosome enzymes.

12.5 Specific Mycobacterial Infections

NTMs are associated with PD, lymphadenitis, skin and soft tissue infections, bone and disseminated infections; Table 12.2 shows the common NTMs associated with the various clinical entities.

Table 12.2 Diseases and common NTM recovered

Disease	Common NTM
Pulmonary	*M. avium* complex
	M. abscessus complex
	M. kansasii
	M. Xenopi
	M. malmoense
Lymphadenitis	*M. avium complex*
	M. scrofulaceum
	M. malmoense
	M. hemophilum
Skin, soft tissue, bone	*M. chelonae*
	M. fortuitum
	M. marinum
	M. ulcerans
	M. abscessus complex
Disseminated	*M. avium* complex
	M. abscessus
	M. chimaera
	M. chelonae

12.5.1 M. avium *Complex Infections*

MAC species, especially *M. avium*, are the cause of most NTM-PD worldwide, accounting for 80% in some countries such as the United States [US], Ireland, and South Korea [6]. *M. avium* is the most common MAC species for pulmonary and nonpulmonary disease in the Americas, Europe, Korea, North and East Japan, while *M. intracellulare* is more common in South and West Japan, Taiwan, and China [15].

The MAC glycolipids are important cell surface antigens which are immunogenic and protect against the host immune response, and the serotype-specific GPL is used to subdivide MAC species in at least 31 serotypes [15]. Some of the serotypes [1, 4, 8, 9] were associated with *M. avium* infection in AIDS patients [16] and serotype 4 was associated with a worse prognosis in PD [17]. *M. avium* GPLs are important for the survival of the bacteria in macrophages and for biofilm formation which allows the organism to persist in the pulmonary mucosa, making it difficult to eradicate [18]. MAC and other NTM are low virulent pathogens which may produce disease by local defect in host defense at the point of entry, i.e., defective clearance from damaged bronchial epithelium after inhalation in patients with chronic lung disease, or immune defects with impaired killing after entry via respiratory or gastrointestinal [GI] route allowing the organism to enter the circulation and disseminate to distant organs. Immune clearance of NTM including MAC requires intact interferon [IFN]-¥-interleukin [IL]-12 axis, effective phagocytosis and intracellular killing with adequate monocyte/macrophage hemopoiesis and circulating CD4+ T cell numbers [19]. CD4+ helper T cells regulate and produce IFN-¥ and disseminated MAC in AIDS patients primarily occurs when the CD4 count is <50 cells/mL. Tumor necrosis factor [TNF]-α also plays an important role in containing the bacteria through development of granulomas [20].

12.5.2 Clinical Disease Associated with MAC

MAC is most commonly associated with PD, lymphadenitis, disseminated infection, and rarely musculoskeletal and cutaneous infection.

MAC is most commonly associated with pulmonary infection or asymptomatic colonization in the presence of chronic lung disease. It can be associated with noninvasive disease or invasive, slowly progressive PD. Occasionally subjects without underlying lung disease may develop bilateral interstitial infiltrates or ground-glass appearance on computed tomography [CT] scan due to hypersensitivity pneumonitis to MAC [hot tub lung] [21]. In patients without immunosuppression MAC PD presents with two distinct radiologic forms: fibrocavitary [FC] and nodular bronchiectatic [NB] [22]. The FC form typically present in older males with chronic lung disease from COPD, previously treated TB, CF, prior pneumonia, etc. with predominantly upper lobes cavities and nodules with slow progression, and symptoms of chronic productive cough, hemoptysis, weight loss with advanced disease, with

or without low-grade fever. The NB form occurs mainly in postmenopausal, non-smoking white female [but also increasingly noted in reports from Asia] without known chronic lung disease, but with Marfan-like features, and imaging shows multiple nodules with areas of bronchiectasis and predilection for the right middle lobe and lingula. Immunosuppressed and AIDS patients sometimes present with multiple nodules and diffuse interstitial infiltrates [23]. The diagnosis of MAC-PD consists of pulmonary symptoms [new or worsening], imaging findings of nodular or cavitary opacities, at least two positive sputum culture for MAC, or a positive bronchial lavage, or lung biopsy showing granulomatous changes and culture of MAC, and exclusion of other explanatory diagnosis [15]. These criteria are also applicable to other NTM-PD.

Disseminated MAC is most commonly seen in advanced AIDS with CD4 count <50 cells/mm^3, but since the advent of highly active ART the rates have dramatically declined in the past two decades [24]. However, with the increased use of immunosuppressive therapy globally in organ transplants, cancers, and autoimmune diseases, disseminated MAC is being increasingly recognized in non-HIV patients [25]. AIDS patients with disseminated MAC usually present with fever, profound night sweats, weight loss/cachexia, diarrhea, severe anemia or pancytopenia, liver disturbance with greater increase in alkaline phosphatase than transaminases, and diffuse lymphadenopathy of the thorax and abdomen on imaging but rarely pulmonary involvement [26]. Diagnosis is usually made by culturing anticoagulated blood in liquid media with a sensitivity of 90% [27].

MAC is the commonest cause of NTM lymphadenitis which is seen mostly in healthy children <14 years of age, especially between 1 and 4 years of age, primarily unilateral involving the anterior cervical nodes [including submandibular and submental nodes] with insidious enlargement, but caseation and rupture to form sinus may occur. Diagnosis can be made by biopsy or aspiration of fluctuant node with caseation and pus. Cutaneous and soft tissue infection, tenosynovitis, septic arthritis, and osteomyelitis rarely occur with MAC following trauma and surgery in normal hosts or in the immunosuppressed [23]. Diagnosis is commonly missed unless biopsy and mycobacterial cultures are done.

12.5.3 Susceptibility Testing and Resistance of MAC

Guidelines recommend that MAC isolates from previously untreated patients should be tested for clarithromycin susceptibility by broth micro- or macrodilution method for baseline values, with susceptible MICs of ≤4 μg/mL and resistance at ≥32 μg/mL [24]. The current guidelines for testing MAC isolates have not changed since 2007 and still recommend susceptibility testing for only macrolides [clarithromycin], even for isolates recovered after treatment failure, recurrence or breakthrough on prophylaxis, as there is poor correlation between in vitro susceptibility results and clinical outcomes with other drugs [except for amikacin]. A recent study reported the MICs distribution for 229 MAC isolates of the main drugs

used in the treatment of MAC infection correlated with PK/PD-derived breakpoints and found 93.5% susceptible to clarithromycin, 9.6% to ethambutol, 3% to rifampin, 15.3% to moxifloxacin, 15.7% for linezolid, and 80.8% for amikacin [28]. Based on this data, ethambutol and rifampin which are commonly used in MAC regimen should not be suitable agents for treatment of MAC. However, susceptibility tests and clinical response correlation have only been demonstrated for macrolides and amikacin in controlled clinical trials [23]. Isolates of MAC with MIC ≥64 μg/mL to amikacin would not respond to intravenous [IV] or >64 μg/mL for inhaled amikacin [29]. A recent study of 83 MAC isolates reported high susceptibility to aminoglycosides [82.7–88%], d-cycloserine [82.7%], clofazimine [97.3%], and clarithromycin [92%] against *M. intracellulare;* and to two aminoglycosides [isepamicin, streptomycin, 87.5%], d-cycloserine [100%], and clarithromycin [100%] against *M. avium* [30].

NTM in general and MAC in particular are intrinsically resistant to many drugs by biofilm formation, most notable in PD, efflux pumps [transporter proteins that extrude antimicrobials], and enzymes that degrade or inactivate antimicrobials. Acquired resistance can be induced by exposure to macrolides by two efflux pumps of MAC [31] and mutations in the *rrl* gene which encodes 23rRNA [15]. Mutations in the codon 2058 or 2059 of the 23S sRNA gene have been associated with high level macrolide resistance in both MAC species and the *M. abscessus* group [32]. Resistance to rifamycins is conferred by mutations in the *rpoB* gene, similar to that in *M. tuberculosis,* while resistance to ethambutol is associated with mutation in the *embB, embR,* and other genes in the *emb operon*, which encodes a target enzyme used in arabinogalactan biosynthesis [15]. Resistance to the aminoglycosides is associated with mutations in the 16S rRNA gene *rpsl* [33].

12.5.4 Treatment of Pulmonary MAC

The decision to treat NTM PD should be weighed carefully and should depend on multiple factors such as age, comorbid illness, prognosis, severity of symptoms and disease on imaging, species of mycobacteria, and phenotype of disease pattern. For elderly patients with mild NB form of MAC which runs a slow progressive course, treatment may not be indicated, as the side effects may be worse than the disease symptoms. Thus the goals of therapy should be considered—improvement or maintenance of quality of life versus prolongation of life.

It is important to consider the natural history of the disease before recommending treatment and involve the patient in the decision making. Few studies, however, have been published on the natural history of MAC-PD, usually retrospective studies on the milder non-cavitary NB form in Asian patients. Two of the larger studies published since 2013 will be reviewed. In a cohort of 265 patients with NB MAC-PD not on treatment followed with serial CT scans, 126 [48%] patients had progression with radiologic deterioration or worsening symptoms requiring treatment in a mean of 32 months [34]. Patients with cavities or consolidation on initial imaging were

likely to progress and require treatment. In a more recent study 551 patients with NB MAC-PD followed for at least 4 years, median of 5.8 years, 323 [58.6%] progressed and required treatment within 3 years, and the remaining 228 [41.4%] remained stable [35]. During a median of 5 years follow-up, spontaneous sputum conversion occurred in 52.2% of patients not requiring treatment. Predictors of progression were age <60 years, positive sputum smear, systemic symptoms, low body mass index [BMI], and ≥4 lobes involvement. In a smaller study of 126 patients, besides low BMI <21 kg/m^2 and high bacterial load on smear, persistence of MAC sputum culture positivity were predictors of radiographic progression [36].

Table 12.3 outlines the recommended treatment for the various forms of MAC infection. The macrolides, clarithromycin or azithromycin, are the main backbone of therapy with ethambutol, rifampin or rifabutin, and aminoglycoside in certain cases. Patients with NB MAC-PD or those with FC-PD unable to tolerate daily therapy are recommended to receive three drugs three times per week [23]. The regimen includes clarithromycin 1000 mg or azithromycin 500–600 mg, ethambutol 25 mg/kg, and rifampin 600 mg three times weekly. In the presence of FC disease the same three drugs are used daily at lower doses for azithromycin [250 mg] and ethambutol [15 mg/kg], but the same dosing for rifampin and clarithromycin. Aminoglycosides are recommended for the first 2–3 months in patients with cavitary [FC] form, macrolide resistance, or treatment failure based on a single randomized study [37]. In this study 146 patients were randomized to receive streptomycin intramuscularly [IM] 15 mg/kg three times per week for 3 months plus standard triple drug regimen or standard therapy alone given for >24 months. Although sputum conversion rate was greater in the aminoglycoside group, there was no

Table 12.3 Treatment of *M. avium* complex infection

Type of disease	Recommended Therapy
Pulmonary MAC	
NB [mild-moderate]	Azithro. 500–600 mg or Clari. 1000 mg 3× weekly plus
	Ethambutol 25 mg/kg 3× weekly plus
	Rifampin 600 mg 3× weekly
Cavitary disease	Azithro. 250–300 mg OD or Clari. 500 mg BID plus
	Ethambutol 15 mg/kg OD plus
	Rifampin 450–600 mg OD plus
	Streptomycin 500–1000 mg or Amikacin 15 mg/kg 2–3× weekly for the first 2 months
Severe or previously treated	Same as for cavitary disease
Disseminated MAC	Azithro. 250–300 mg OD or Clari. 500 mg BID
	Ethambutol 15 mg/kg OD
	Rifabutin 300–450 mg OD plus ART for HIV
Prophylaxis for disseminated MAC	Azithro. 1200 mg once weekly or Clari. 500 mg OD or BID

NB nodular bronchiectatic disease, *Azithro.* azithromycin, *Clari.* clarithromycin, *OD* once daily, *BID* twice daily, *ART* antiretroviral agent. See [23]

significant difference in clinical or radiologic response and sputum relapse rate. In a recent retrospective study patients who received streptomycin for ≥3 months had significantly higher success, sputum conversion greater than those treated with <3 months [69.3% vs 46.2%] [38]. The duration of standard 3 drug regimen is 12 months beyond sputum conversion [39]. With respect to thrice weekly versus daily treatment for NB-PD, a retrospective cohort study of 217 patients found similar rates of sputum conversion, which supports the recommendation [40].

Clofazimine, an old drug used for leprosy since the 1950s, has good in vitro activity against MAC and other NTM [30, 41] and has been used in combination with macrolide and ethambutol [42]. In a retrospective study of 107 patients with MAC-PD, 25% with cavitation, combination with CFZ resulted in conversion to negative sputum greater than combination with rifampin [100% vs 71%, $p = 0.0002$] [43]. Thus, a randomized, prospective, controlled study is indicated to compare standard triple therapy with rifampin versus triple therapy with CLZ in MAC-PD.

It should be noted that most, if not all, studies define favorable outcome based on sputum culture conversion after initiation of therapy and maintenance of a negative sputum culture ≥12 months. In a recent report of 481 patients who underwent treatment, favorable outcome occurred in 88% with non-cavitary disease compared to 76% with FC disease [44]. However, if treatment success is defined as eradication of the organism without relapse for several years after discontinuation of treatment, then treatment success is about 55% based on a review of 38 reports [45]. In a more recent review and meta-analysis, using the standard criteria of treatment success, macrolide containing regimens are relatively poor with regards to treatment success and default rates [46]. In 16 studies involving 1462 patients, the rate of treatment success was 60.0% with 16% default of therapy [12% with thrice weekly] and severe adverse events from macrolides were found in 6.4% and decreased hearing was the most common. The default and severe adverse event rates reported from this review are surprisingly low. In a recent open label randomized study of three- versus two-drug regimen [clarithromycin/ethambutol/rifampin vs clarithromycin/ethambutol], the default rate in the 3-drug regimen was 45.7% with severe reaction in 37% versus default rate of 33.3% and significant adverse event in 26% in the 2-drug arm [47]. This study initially had 59 patients assigned to 3-drugs with only 32 completing the study versus 60 patients assigned to 2-drugs with 40 completing the study. Surprisingly only 40.6% of the 3-drug arm had sputum conversion versus 55.0% in the 2-drug group with similar rates of cavitary disease. However, the high drop-out rates make these results invalid.

12.5.4.1 Issues and Controversies of Pulmonary MAC Treatment

There is no significant large double-blind, placebo, controlled trial in MAC-PD to prove that any treatment makes a difference in the clinical outcome. Using sputum conversion rates for comparing response is not an adequate end-point, especially since MAC and NTM in general are not contagious and reinfection with different strains in patients with chronic lung disease is common. In one study patients with

persistently positive sputum after ≥12 month therapy, genotyping revealed that this was due to reinfection with new MAC strains in 73% and macrolide resistance was present in 22% [48]. Comparative clinical trials in the future in MAC-PD should use composite endpoints [49], such as clinical response or stabilization, radiographic progression, sputum conversion, pulmonary function deterioration, all-cause and MAC-PD related mortality. In a large cohort of 782 patients with NB MAC-PD, radiographic deterioration occurred in 41.2% at a median time of 9 years and only 2.4% died from progression of MAC-PD [50].

Future research and clinical trials are needed to assess for more effective combination therapy for MAC-PD, especially for a finite period of time. Too often in clinical practice and drug trials patients are on multiple drugs for 24–36 months, without any clear evidence of clinical benefit or decrease in mortality. Suitable combinations for clinical trials may be selected from results in the hollow-fiber system model. In a recent study using this model, the backbone combination azithromycin and ethambutol had poor MAC kill rates and was ineffective with ethambutol resistance occurring in 100% of the bacterial population by day 28 [51]. A combination of standard oral drugs with inhaled aminoglycoside should be studied for all MAC-PD given for a finite period. Inhaled amikacin liposome for refractory MAC-PD appears promising in a preliminary randomized, open label trial [52]. MAC-PD is difficult to treat because of the underlying chronic lung disease and biofilm infection in the lungs. High concentration of inhaled drugs would have a better chance of clearing the infected biofilm and it would be worthwhile comparing combination of inhaled drugs to standard systemic therapy.

12.5.5 Treatment of Disseminated MAC

Disseminated MAC [DMAC] has declined dramatically since the advent of highly effective combination ART [cART] in 1996, but advanced HIV-infection is still the main cause. Recent reports, even from countries with low endemic HIV rate, found that DMAC is related to HIV-infection in most patients and non-HIV immunosuppressed conditions are accounting for an increasing proportion. In a retrospective study from a single center, 330 HIV-infected patients were diagnosed with DMAC from 1992 to 2015 with incidence declining from 65.3/1000 in 1992 to 2.0/1000 in 2015 [53]. For patients diagnosed with DMAC in or after 2000, 20% were newly diagnosed with advanced AIDS and 80% had longstanding known HIV who failed to continue consistent medical care with progression to late stage disease.

The treatment guidelines of DMAC include clarithromycin [500 mg twice daily] or azithromycin [500–600 mg daily], ethambutol [15 mg/kg daily] with or without rifabutin [300–450 mg daily], plus starting cART as soon as possible [39]. In the recent report of 24 patients with DMAC in HIV, 79% of those newly diagnosed with DMAC and prescribed cART developed the immune reconstitution syndrome [IRIS], eight paradoxical and 11 unmasking, with a mortality of 29% [54]. Most

patients with MAC-IRIS can be treated with nonsteroidal anti-inflammatory agents [NSAIDS] or steroids and there is no good data that cART should be delayed. Some guidelines recommend triple therapy over the two-drug regimen to decrease the risk of developing macrolide resistance. In a randomized, placebo-controlled trial of DMAC in HIV, adding rifabutin to clarithromycin and ethambutol did not improve response or survival, but decreased macrolide resistance from 14% to 2% [$p = 0.055$] [55]. Another randomized trial of 2- versus 3-drugs for DMAC showed improved survival by several months of the 3-drug arm, but no difference in clinical or microbiological response [56]. Drug interactions with rifabutin and clarithromycin are of concern and high dose of rifabutin [>450 mg/day] has been associated with uveitis.

Refractory infection or relapse of DMAC is mainly due to inadequate control of HIV-infection from noncompliance or resistant strain of HIV and rarely from macrolide resistant MAC from previous prophylaxis. Addition of two new agents with activity to MAC has been suggested but no data is available [23]. Adding amikacin [15 mg/kg/day] [23] and moxifloxacin may be a consideration and susceptibility to ethambutol and fluoroquinolones is warranted in patients with persistent MAC bacteremia [57]. In HIV patients MAC therapy can be stopped once the CD4 count is ≥150 cells/μL for 3–6 months on cART based on observational data. DMAC still carries a high mortality in HIV patients even with cART, mainly from the profound immunosuppression with persistently low CD4 count [53]. The median survival of patients with DMAC who never received cART was found to be 189 days and of those who start cART 60% were still alive at 454 days follow-up, with 25% alive post-DMAC at 5 years and only 7% alive 10 years post-DMAC diagnosis [53].

MAC prophylaxis for HIV patients with low CD4 count ≤50 cells/μl should no longer be necessary with azithromycin [1200 mg/week] or clarithromycin [1000 mg daily], once cART is being initiated as the risk of DMAC is only 10% per year [58] and the CD4 count will usually increase ≥100 cells/μL after 3 months therapy. However, secondary prophylaxis should be considered in non-HIV patients treated for DMAC and maintained on immunosuppressive agents due to high recurrence rate [59]. Data on treatment of DMAC in non-HIV immunosuppressed patients are sparse, but treatment usually includes triple drugs for 12–24 months and reduction on immunosuppressed agents [59]. Treatment of refractory, disseminated NTM infection in seven patients with addition of IFN-¥ has been reported to be effective [60], but it is very likely these patients had unrecognized impaired IFN-¥ pathway secondary to genetic mutations.

12.5.6 Treatment of Localized Non-pulmonary MAC

Mycobacterial cervicofacial lymphadenitis is most commonly due to NTM in children and TB in adults. MAC is the most common cause of NTM cervical lymphadenitis and other causes include *M. scrofulaceum, M. malmoense, and M. haemophilum* [61], *M. kansasii*, and others. MAC rarely causes cervical or extrapulmonary disease in immunocompetent adults. In large surveys of mycobacterial infections of

adults, MAC cervical lymphadenitis accounted for <1–3% [62]. Studies from Europe, Australia, and New Zealand have found incidence rates of NTM lymphadenitis in children <15 years of age of 0.42–0.88 cases per 100,000, with MAC being the commonest [63].

The treatment of NTM [including MAC] cervical lymphadenitis in children has largely been by surgical excision with recurrence rate of <1% [64]. In a randomized, controlled, multicenter study comparing surgical excision versus antibiotic therapy, cure rates were 96% versus 66% in favor of surgery [65]. However, surgical complications were seen in 28% and antibiotic therapy resulted in adverse events in 78% of those medically treated. Temporary facial nerve weakness was reported in 20% and permanent facial weakness in 2%. Hence, observation with no intervention is an option for children with a confirmed diagnosis. In an exploratory randomized trial, 50 children [25 in each group] received either a 12 week course of clarithromycin and rifabutin or observation only [66]. The median time to resolution of the disease was 35 weeks with antibiotics and 40 weeks for the observation group, with total resolution of the lymphadenitis achieved in 71% within 6 months without antibiotics.

Data on treatment of soft tissue, bone, and joints infections with MAC are limited. Debridement of tissue and drainage of joints and abscesses are usually performed and standard triple-drugs with macrolide are commonly used for ≥6 months, and parenteral aminoglycoside with refractory infection [23].

12.6 Mycobacterium Abscessus Infection

M. abscessus complex comprise a group of rapidly growing mycobacteria [RGM] of low virulence that are capable of causing a wide-spectrum of diseases. Recovery of rapidly growing mycobacteria [or any NTM] from clinical specimens may or may not be of clinical significance, but could represent laboratory or instrument contamination or colonization. *M. abscessus, M. fortuitum* and *M. chelonae* are the most important RGM, but *M. abscessus* is the most difficult to treat because of extensive drug resistance and was separated from *M. chelonae* group in 1992.

12.6.1 In Vitro Susceptibility of M. abscessus

The CLSI recommend testing clinical significant RGM against amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline or minocycline, imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole [TMP-SMX], and tobramycin [M. chelonae/immunogenum complex only] [29]. Identification to species and subspecies level [especially for *M. abscessus* complex] is preferable for selection of treatment. Although the MALDI-TOF is now commonly used in many clinical laboratories, it is not suitable for subspecies identification of

Table 12.4 Antimicrobials MIC breakpoints for rapidly growing mycobacteria

	MIC (μg/mL)		
Antimicrobial agent	Susceptible	Intermediate	Resistant
Amikacin	≤16	32	≥64
Tobramycin	≤2	4	≥8
Cefoxitin	≤16	32–64	≥128
Clarithromycin	≤2	4	≥8
Clofazimine[a]	<1		≥1
Ciprofloxacin[b]	≤1	2	≥4
Imipenem[c]	≤4	8–16	≥32
Linezolid	≤8	16	≥32
Minocycline	≤1	2–4	≥8
Rifabutin	<1		≥1
Sulfamethoxazole	≤38		≥76
Tigecycline	≤4		≥4

Data obtained from [67, 68]
[a]Some reference set the resistance breakpoint at ≥2
[b]Indicate moxifloxacin breakpoints the same
[c]Indicate meropenem breakpoints the same

M. abscessus complex and this requires gene sequencing method [29]. Breakpoints for the various drugs are shown in Table 12.4.

Data on susceptibility patterns of the RGM have been limited by the small number of isolates tested for the various species or subspecies. Overall, *M. abscessus* is the most resistant, followed by *M. chelonae,* and *M. fortuitum*. Previous studies before 2005 found that *M. abscessus* isolates were commonly susceptible to amikacin, clarithromycin [or azithromycin], cefoxitin, and imipenem; *M. chelonae* usually inhibited by the macrolides, linezolid and tobramycin; and *M. fortuitum* frequently inhibited by tetracyclines, TMP-SMX, and quinolones [69]. However, it is important to review the results of more recent studies to determine any changing pattern. A study from Texas in 2007 reported the susceptibility of 105 RGM, 40 *M. abscessus* strains, 31 *M. fortuitum* strains, and 25 *Mycobacterium mucogenicum* strains [70]. Among *M. abscessus* strains, amikacin and clarithromycin were the most active agents [95% and 98% susceptible], followed by imipenem [77% susceptible or intermediate with 17.5% fully susceptible], and cefoxitin [75% susceptible or intermediate with 15% fully susceptible]. For *M. fortuitum* strains, all were susceptible to ciprofloxacin, 81% susceptible to imipenem and 71% susceptible to TMP-SMX; less than 50% were susceptible to doxycycline and only 29% susceptible to the macrolides. *M. mucogenicum* strains [the commonest cause of RGM bacteremia in this study] were susceptible to cefoxitin, clarithromycin, imipenem, and TMP-SMX, with 88% susceptible to ciprofloxacin and 50% to doxycycline [70].

More recent studies have been reported from Asia but usually with low numbers of strains per species. In a study from Japan, 42 RGM isolates were tested: 13 *M. abscessus* strains, 12 *M. chelonae* strains, and 17 *M. fortuitum* complex strains [67]. Among *M. abscessus* strains the most active agents were amikacin and

tigecycline [100% susceptible], followed by linezolid [76.9% susceptible], clarithromycin [61.5% susceptible], and imipenem [30.8% susceptible and 69.2% intermediate]. Among *M. chelonae* the most active agents were clarithromycin, linezolid, and tigecycline [100% susceptible], followed by amikacin [91.7% susceptible], tobramycin [83.3% susceptible], and imipenem [58.3% susceptible with 41.7% intermediate]. For *M. fortuitum* strains the most active agents were quinolones and tigecycline [100% susceptible], followed by linezolid [86.6% susceptible], amikacin [80% susceptible], imipenem [80% susceptible], minocycline [33.3% susceptible], and almost all strains were macrolide resistant except two strains of *M. peregrinum* subspecies [67]. Two recent studies have been published from China with some variability in results between the two centers [68, 71], thus the data were combined to provide an overall picture of the susceptibility results. There were only three isolates of *M. chelonae* tested and these results are not included. A total of 75 strains of *M. abscessus* and 28 strains of *M. fortuitum* were tested in the two studies. For *M. abscessus* the most active agent was linezolid [92% susceptible], followed by amikacin [85.3% susceptible], tigecycline [78.65 susceptible], and cefmetazole [73.3% susceptible]. For *M. fortuitum* the most active agent was tigecycline [92.8% susceptible], cefmetazole [85.7% susceptible], imipenem [71.4% susceptible], levofloxacin [63.3% susceptible], and TMP/SMX [46.4% susceptible]. Interestingly, whereas rifampin has poor activity against the RGM, 49.3% of *the M. abscessus* strains were susceptible to rifabutin. This is similar to a recent report which found all *M. abscessus* reference subspecies [nine strains tested] were susceptible to rifabutin but rifampin resistant [72]. In another study of 67 strains of *M. abscessus*, clofazimine and tigecycline were the two most active agents and the combination of these two agents were synergistic in 42% of the isolates tested [73]. Others have also shown high activity of clofazimine against 117 isolates of *M. abscessus* with synergism with amikacin [74], but a recent study found that the majority of *M. abscessus* and *M. fortuitum* had MICs higher than 2 μg/mL [susceptible <1 μg/mL], and only 17 out of the 30 reference strains of RGM species had MICs <1 μg/mL [41].

M. abscessus complex [MABC] is intrinsically resistant to many drug classes and has the ability to inactivate many antibiotic classes through antibiotic-modifying enzymes [75]. Also the susceptibility to antimicrobials varies with the subspecies which is rarely reported in most studies on in vitro susceptibility. More recent studies have investigated the in vitro activity of combinations and new classes of antibiotics. One such study reports high activity of dual β-lactam combination, ceftazidime with either ceftaroline or imipenem, with synergism [76]. This may be explained by a previous study which found that MABC transpeptidases are susceptible to inactivation by cephalosporins and carbapenems [77]. However, chromosomally encoded β-lactanases, Bla_{Mab}, can inactivate several β-lactams and is not inhibited by common β-lactamase inhibitors [BLI], clavulanate, tazobactam, and sulbactam [78]. Avibactam is the most effective BLI against MABC that have been shown to potentiate β-lactams activity in vitro and in vivo models, but best studied and shown to improve the killing of MABC in combination with imipenem [79]. However, avibactam is not available by itself and is coformulated as ceftazidime/avibactam

which is approved by FDA for nosocomial resistant gram-negative bacilli. Although this combination has been shown to be effective for resistant TB and MAC [80], there is no reported study to date of its activity against MABC but it is likely to be effective.

12.6.2 Macrolide Mutations Among M. abscessus *Complex*

It is necessary to perform the *rpoβ* gene sequencing to identify the subspecies of MABC. *M. abscessus* subsp. *abscessus* is more common in North America and 80% carry the *erm* gene which predicts inducible macrolide resistance and about 20% of the isolates have nonfunctional *erm* [29]. *M. abscessus* subsp. *massiliense* is more frequently seen in Korea, lacks the inducible gene or a truncated *erm* gene; in contrast *M. abscessus* subsp. *bolletii* have a functional *erm* and should be considered macrolide resistant [most studies from Asia] [29]. Macrolide resistance in *M. abscessus* complex, similarly to MAC, may also develop from mutation in the 23S rRNA gene. Amikacin resistance can also occur in *M. abscessus* and *M. chelonae* from a single mutation in the 16S rRNA [81]. *M. fortuitum* are intrinsically resistant to the macrolides due to functioning *erm* gene [82].

12.6.3 Clinical Aspects of M. abscessus *Infection*

The global burden of *M. abscessus* complex [MABC] disease is unknown due to limitations in speciation of NTM in many countries and medical centers around the world. It is most commonly associated with pulmonary disease in patients with chronic lung diseases [bronchiectasis, CF, etc.] similar to MAC, or immunosuppression; surgical wound infections [mammoplasty, facial plastic surgery, cardiac surgery] and post-injection abscesses; post-traumatic skin and soft tissue infections from soil or water contamination, and can mimic infection with sporotrichosis with ascending lymphadenitis, but primary lymphadenitis is rare; ocular infection with keratitis, scleritis, or endophthalmitis; rarely meningitis or brain abscess; rarely disseminated infection in the immunosuppressed with metastases to bone/joints, sometimes with multiple draining erythematous cutaneous nodules; and rarely bacteremia/endocarditis in hemodialysis patients or cardiac surgery [83, 84]. The clinical spectrum of MABC infection, risk factors, and relative proportion of the clinical entities are represented in a study from Miami of 108 patients: 10.2% with renal failure, 31.5% on immunosuppression, and 40% had chronic lung disease; 54.6% of isolates from respiratory sources, 19.4% from blood, 9.25% from skin/soft tissue, and 8.3% from intra-abdominal source [85].

In the United States [US] *M. abscessus* complex is second only to MAC infections, representing 2.6–13.0% of all mycobacterial pulmonary infections, <1 per 100,000 population, but the prevalence is increasing [81]. *M. abscessus* infections

appear to be more prevalent in East Asia, comprising 17.2% of all NTM isolated with 1.7 cases per 100,000 population in Taiwan [86]. In most studies *M. abscessus* subsp. *massiliense* and subsp. *abscessus* are most commonly found and subsp. *bolletii* is rarely isolated [87]. In North America *M. abscessus* subsp. *abscessus* is more commonly seen, often resistant to macrolides due to presence of the *erm* gene, while *M. abscessus* subsp. *massiliense* which lacks the *erm* gene is more commonly seen in Asia, i.e., Korea [John Hopkins ABX guide].

MABC is most commonly associated with pulmonary disease in vulnerable subjects with underlying chronic lung disease such as CF, bronchiectasis, and previous TB [83]. MABC-PD is usually an indolent, progressive disease with persistent symptoms and slow decline of pulmonary function, but occasionally can present with a fulminant course with respiratory failure [83]. The diagnosis of MABC-PD is similar to other NTM-PD with a combination of symptoms, imaging findings and at least two separate sputum cultures growing MABC. This mycobacteria is a particular problem in CF and it represents the commonest cause of NTM infection in CF patients in Europe, with evidence of human-to-human transmission, producing decline in lung function and difficult to treat [88, 89]. MABC is no longer a contraindication for lung transplant in CF, but postoperative complications are great and prolonged aggressive treatment is needed [90].

Drug susceptibility testing and PCR to detect the inducible macrolide resistant *erm* gene is recommended to guide therapy for MABC infection. Unlike NTM-PD such as MAC, there is no antibiotic regimen that has demonstrated sustained long-term sputum culture conversion in patients with MABC-PD and cure [>12 months negative sputum cultures] may be unattainable compared to long-term goal of clinical control [91]. An initial induction phase with one or more intravenous [IV] agents for at least 8 weeks depending on tolerance; then a consolidation phase with oral or inhaled agents for 12–18 months; followed by suppressive phase in patients at high risk of relapse [91]. In a large study of MABC-PD treated with the same regimen, sputum conversion was much greater in *M. massiliense* infected group [88%] than in the *M. abscessus* subsp. group [25%] [92]. For macrolide susceptible strains [*M. massiliense*] an oral macrolide should be included in all phases; and for macrolide-resistant strains [*M. abscessus* subsp.] an oral macrolide may still be considered but this is controversial [93]. There is limited data in a small number of patients that azithromycin is better than clarithromycin, besides better tolerability with single daily dose, but may be less likely to induce the *erm* gene [94].

Data on the treatment of extrapulmonary MABC are scanty but recommendations have been made based on compilation of results from small studies [83]; see Table 12.5. The most commonly used IV drugs include amikacin [25 mg/kg 3×/week], imipenem [500 mg 2–4×/week] and cefoxitin [up to 12 g/day given in three to four divided doses], and more recently tigecycline. Oral agents include azithromycin [250–500 mg daily] or clarithromycin [500 mg twice daily], occasionally quinolones, linezolid, and clofazimine, depending on susceptibility.

For MABC-PD or severe extrapulmonary disease in the immunosuppressed, most guidelines recommend an induction phase of 2–8 weeks with 2–3 IV antibiotics plus a macrolide, then a consolidation phase with 2–3 active oral or inhaled

Table 12.5 Recommended treatment of *M. abscessus* complex infections

Disease	Initial regimen	Maintenance	Duration
Pulmonary	Macrolide, cefoxitin or imipenem + amikacin × 2 wks to 2 mths	Macrolide + other oral active agent[a]	Sputum neg. × 12 mths
Skin/soft tissue	Macrolide + amikacin + cefoxitin or Imipenem × 2 wks/debridement	Macrolide + oral agent	Minimum 4 mths
Bone	Same regimen	Same	6 mths
Bacteremia	Amikacin [2 wks] + macrolide remove catheter	Two active agents	4 wks after last +ve culture
Disseminated			
Deep ocular	Macrolide + amikacin or imipenem + surgery [IV 2–6 wks]	Two active agents	6 wks to 6 mths
CNS	Macrolide + imipenem + amikacin × at least 1 mth plus surgery	Macrolide + other oral active agent	12 mths

Reference: see [39, 83, 95]

CNS central nervous system, *IV* intravenous, *neg.* negative, *mth* month, *wk* week

[a]Other oral active agents may include rifabutin, clofazimine, quinolone, linezolid—should be based on susceptibility. Tigecycline IV can be used for multiresistant or macrolide strains

antibiotics for 12–18 months, and suppressive phase in some patients with two active oral/inhaled antibiotics [91]. Amikacin and clarithromycin and possibly tigecycline are commonly used together in the induction phase. However, an in vitro study recently showed that clarithromycin can induce resistance to amikacin and tigecycline during incubation with a *M. abscessus* ATCC strain, through the induction of the *whiB7* gene [96]. Recent guidelines for therapy of MABC have listed clofazimine and linezolid as options for therapy based mainly on in vitro data. The clinical experience with clofazimine is largely for treatment of leprosy and more recently it has been used in regimens for multiresistant TB. A recent observational-cohort study assessed clofazimine for pulmonary and extrapulmonary disease as part of a multidrug regimen in 122 patients, 54 with MABC and 41 with MAC and 78% were refractory or failed other therapy [97]. The median duration of clofazimine use was 383 days, 14% stopped the drug due to adverse events after a median of 101 days, and 41 of 82 [50%] patients with PD converted to negative sputum cultures within 12 months.

Linezolid is listed as potential oral agent in combination with others for consolidation therapy [91], John Hopkins ABX Guide, depending on susceptibility results, but there is no clinical data on its value or tolerance for MABC infections. Long-term risks of linezolid include cytopenias, neuropathy, and optic-neuritis [John Hopkins ABX Guide]. A new related antibiotic to linezolid, tedizolid, recently FDA-approved appears to be a more suitable agent for MABC infection. It is more active than linezolid against NTM isolates with MIC values 2–8 times more active, single daily dosing and lower incidence of side effects, but there is little experience with long term use [98]. Based on recent in vitro data, rifabutin should be considered for MABC treatment in the induction or consolidation phases of treatment for very resistant strains, despite the universal resistance against rifampin [99]. This drug has been on the market for many years and has been studied in HIV patients

with disseminated MAC. A dose of rifabutin 300 mg daily appears to safe for long-term use, but 600 mg daily may result in uveitis. Bedaquiline, a new antimycobacterial agent, being used for drug-resistant TB has been used in refractory MAC and MABC disease with some benefit [100].

12.6.4 Recent Clinical Studies on Treatment of M. abscessus *Infection*

The clinical response to recommended treatment for MABC-PD or severe extrapulmonary infections is ill-defined or unclear. In a hollow-fiber model of MABC-PD, with standard amikacin, clarithromycin, and cefoxitin combination and drug exposures similar to those achieved in the lungs of humans, after initial killing in the first 14 days there was regrowth with acquired drug resistance [101]. A recent systematic review and meta-analysis of the effect of standard therapy on MABC-PD on outcomes have been published. The review included 19 studies of 1533 patients, combination therapy was given to 508 subjects with *M. abscessus* subsp. *abscessus*, 204 with *M. abscessus* subsp. *massiliense*, and 301 with *M. abscessus* species unspecified [102]. Macrolide combination regimens only achieved sputum conversion in 34% of subspecies *M. abscessus* and 54% of *M. massiliense,* with good outcomes in 23% of patients with *M. abscessus* subspecies and 84% with *M. massiliense*. Thus, the current recommended combination therapies for PD with subspecies *M. abscessus* are poor and new treatment should be explored. In a study from South Korea of 67 patients with MABC-PD sputum conversion occurred in 51% with treatment, but in patients with persistent positive sputum or recurrences, genotypic analysis revealed that 92% were caused by different *M. abscessus* genotypes within a patient [103]. The results of the systematic review are similar to an even more recent report from a single center in China of MABC-PD. In this study 244 patients were included and only 45% achieved treatment success, 81.4% with *M. massiliense* compared to 33.5% with M. subsp. *abscessus* [104]. Of note, similar to other reports, 78.7% experienced side effects [most commonly gastrointestinal distress] and 24.6% resulted in discontinuation or modification of therapy. Logistic regression analysis indicated that azithromycin was superior to clarithromycin and treatment success correlated with the use of amikacin, imipenem, linezolid, and tigecycline.

There is a paucity of data on extrapulmonary MABC infection response to treatment, most appropriate regimen and duration of therapy. Most reports included small number of cases and used therapy recommended for MABC-PD or based on susceptibility with various durations. The Emerging Infections Network reported on 24 extra-pulmonary MABC infections [71% due to skin/soft tissue infections], mainly treated with amikacin, macrolides and imipenem with median duration of 6 months, but 67% of cases required change in therapy [105]. Fourteen [58%] patients required surgery and 58% also completed therapy after improvement or presumed cure. Disseminated MABC infections are extremely rare and are reported

in immunosuppressed states as in organ transplant and autoimmune diseases being treated with corticosteroids. A review of the literature from 1953 to 2014 found only 34 reported cases, plus the case presented [106]. RGM bacteremia is also very rare, mainly reported from large cancer centers and most cases [96%] are due to central venous catheter infections and occasionally from cardiac implant/prosthesis infection. In a series of 119 cases of RGM bacteremia from a large cancer center, *M. mucogenicum* was the commonest cause [39%], followed by *M. fortuitum* [21%], and MABC [14%] [107]. Removal of the catheters and 4 weeks antibiotic therapy produced good results. MABC bacteremia was reported from the National University hospital in Taiwan over 7 years in 15 patients with various conditions: steroid usage/malignancy [33.3%], diabetes [26.7%], and surgical wound infection [33.3%] was the commonest source [108]. Treatment most commonly included imipenem, amikacin, and clarithromycin with a 14-day mortality of 20%; however, the majority of isolates were the more susceptible *M. bolletii* subspecies.

The outcome of extra-pulmonary MABC-infections depend on the underlying conditions, severity of disease, type of infection and the subspecies with presence of functional macrolide resistant gene. This is reflected in the report from South Korea of 20 patients with MABC extra-pulmonary infection: most with no underlying disease: 35% due to skin/soft tissue infection, 30% with bone/joint infection and 35% with ocular [mainly superficial] infection [109]. Favorable outcome occurred in 85%, including all with *M. massiliense* infection and 70% with *M. abscessus* infection; thus, response was associated with the subspecies and *M. abscessus* with non-functional *erm* gene. Treatment varied with oral antibiotics for a median duration of 177 days and combined oral/IV therapy for median duration of 27 days.

12.7 Mycobacterium Chimaera Infection

M. chimaera is a slow-growing NTM species belonging to the *M. avium* complex that was first described in 2004 and is usually misidentified as *M. intracellulare.* Differentiation requires the sequencing of the 16-23S internal transcribed spacer region [110]. *M. chimaera* was rarely reported to cause disease in patients with chronic lung disease, until a global outbreak of invasive disease was recognized after open-chest heart surgery in 2014 [111]. As of September 2017, ≈120 cases have been reported globally after cardiac surgery from Switzerland, the Netherlands, Germany, UK, US, Australia, New Zealand and more recently Canada [112, 113]. Investigations revealed that *M. chimaera* aerolized from contaminated heater-cooler units [HCUs], to date all the cases were associated with LivaNova 3T HCUs, and settle on surgical instruments, open wounds, or on implant surfaces [113]. Studies using whole genome sequencing and other genetic methods implicate a point source outbreak of a clonal strain of *M. chimaera* related to the one manufacturer's device causing the majority of the cases [113]. Contamination of the HCUs appears to occur during production of the device, as water from the pump assembly area grew the mycobacteria, and although only one brand has been implicated in the

international outbreak, various other HCU brands were found to harbor *M. chimaera* [113, 114]. Most 3T HCUs manufactured in the past decade were contaminated with the same *M. chimaera* strain [115]. *M. chimaera* is of low virulence and preferentially infect prosthetic devices where it forms a biofilm. The earliest date of surgery linked to the outbreak was 2008 and the longest interval from surgery to clinical manifestation has been 6 years [116]. The 3T HCUs has been use since 2006 with 60% of the market share and although the manufacturer made changes in its cleaning and disinfection procedures in September 2014, some 3T devices were tested positive for *M. chimaera* after the change [116].

12.7.1 Clinical Aspects of Invasive M. chimaera *Infections*

Most infected patients with *M. chimaera* had heart valve replacement or cardiac devise implant [grafts, left ventricular assist device [LVAD]] with the use of the 3T HCU in the OR during cardio-pulmonary bypass [117, 118]. However, *M. chimaera* cases have occurred after transcatheter aortic valve replacement [TAVR] which does not require cardio-pulmonary bypass, presumably due to contamination of the devise prior to implantation from a contaminated OR [116]. Thus, all patients undergoing surgery with the HCU running are potential candidates for getting *M. chimaera* infection.

The manifestation of *M. chimaera* infection is diverse and often insidious and nonspecific. Patients may present with prolonged fever with evidence of prosthetic valve infection, considered to be culture negative endocarditis, or localized signs of LVAD infection, sternal wound infection, or aortic-graft infection; but may have non-cardiac manifestation such as pulmonary symptoms and signs mimicking sarcoidosis; evidence of spondylodiscitis and chorioretinitis resembling autoimmune diseases or vasculitis, or presenting with fever and systemic disease of unknown cause [118]. All cases in the US with the disseminated form of disease with liver, spleen, bone marrow, kidney, eye, bones, and joints had prosthetic material in place; but those infected after coronary artery bypass grafting only had locally invasive disease [sternal wound, mediastinum, or pleura] without dissemination [116].

In the largest series [$n = 30$] fever and malaise [80%] were the commonest symptoms, then weight loss [60%], cough [37%], and dyspnea [33%] [119]. Splenomegaly and chorioretinitis may be found and eye examination should be performed in all patients, as the extent of ocular disease correlated with the degree of systemic infection [120]. Lab abnormalities may include cytopenias, elevated transaminases and creatinine, and histopathology of tissues revealed granulomatous reaction with presence of hepatitis, nephritis, myocarditis, pneumonitis, osteomyelitis, chorioretinitis, myositis, and endocarditis [120]. These findings often mimic sarcoidosis and presumptive diagnosis of sarcoidosis was made in 14 of the published cases [120].

12.7.2 *Diagnosis* of M. chimaera *Infection*

The diagnosis of *M chimaera* infection is often difficult due to the long latency [<1 month to 6 years], insidious nature and nonspecific manifestations. The diagnosis can be made from special blood [heparinized] cultures for mycobacteria or tissue samples obtained by biopsy or intraoperatively, but culture may take 2–8 weeks. Presently, most laboratories will identify the NTM as MAC species and precise species identification and susceptibility require a reference laboratory. Rapid and reliable molecular methods for diagnosis have been tested. The TaqMan quantitative polymerase chain reaction [PCR] is more sensitive than culture and can detect low concentration [100 colony-forming units per milliliter of blood] [121]. More recently it has been shown that a novel plasma-based next generation sequencing [NGS] test can detect *M. chimaera* in the blood of nine of ten patients [90%] with invasive disease in a median of 4 days, including all eight patients with disseminated disease and one of two patients with localized disease [122]. In the 24 mycobacterial blood cultures obtained in this study, only four [17%] were positive at a median of 20 days and median time of 41 days for confirmation of *M. chimaera;* whereas NGS was the first test to confirm the species in seven of nine cases [78%].

12.7.3 *Management of* M. chimaera *Infection*

The success of treatment of *M.chimaera* infection requires the removal of infected devises [including prosthetic valves], surgical debridement and prolonged antimycobacterial therapy [118], but the most appropriate combination and duration of therapy is unknown. The mortality in this outbreak was quite high, 46–63% [120], which may be a reflection of late diagnosis with advanced disseminated disease. Patients may initially respond to medical therapy with later relapse and multisystem failure, especially in delayed surgical intervention. Most reports based therapy on guidelines for MAC-PD, as there is sparse data on *M. chimaera* specific susceptibility to various antibiotics.

A recent study has reported the antimicrobial susceptibility of 87 clinical and environmental *M. chimaera* isolates [123]. All isolates were susceptible to clarithromycin with a median MIC of 2 μg/mL, 98% amikacin susceptible [similar for streptomycin], 18% rifampin resistant but 2% rifabutin resistant; 11% ethambutol resistant, 52% moxifloxacin resistant and 25% intermediate susceptible, and 39% linezolid resistant with 39% intermediate susceptible. A recent review suggested treatment regimen of a macrolide, rifamycin, ethambutol, and moxifloxacin or clofazimine, with initial parenteral amikacin; and to consider surgery after 4–6 weeks of therapy [120]. Based on the recent in vitro, it is my opinion that the most suitable treatment regimen for invasive *M. chimaera* infection should include azithromycin [or clarithromycin], rifabutin, ethambutol, and parenteral amikacin for the first month [clofazimine may be used for ethambutol resistant strains]; but to perform

revision surgery within the first 2 weeks to facilitate rapid control and cure of the infection. Treatment should be given for at least 6 months and until there is evidence of resolution of the infection.

12.7.4 Prevention of M. chimaera *Infection*

Presently there is no sustainable method proven to prevent contaminated bioaerosols from HCU in the OR during cardiac surgery. Intensified maintenance protocol with daily water changes failed to prevent contamination with *M. chimaera* from water samples [113]. Successful decontamination has been achieved for 3 months after a comprehensive program: initial mechanical removal of biofilm, replacements of HCU parts, and two consecutive peracetic acid disinfection cycles; then intensified maintenance with daily water changes with filtered tap water and added hydrogen peroxide, and weekly peracetic acid disinfection cycles [124]. This approach seems to be very promising but long term data beyond a year is needed to verify the sustainable efficacy. A purpose-built air-tight encasing for the 3T HCU directly connected to the ventilation system in the OR has been produced, but this requires technical assessment of the overall air flow management to be well tolerated [113]. HCUs have also been outplaced in an adjacent room, but tubing length is a limiting factor and an ajar door may allow bioaerosols to float back into the OR [125].

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