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Review Article

Epidemiology of hepatitis C in Europe

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ABSTRACT

The advent of potent and safe direct-acting antivirals against the hepatitis C virus has the potential of fulfilling the dream of eliminating this infection and its impact on global public health. However, even if effective drugs are at hand, most patients remain unaware of their infection, which may be recognized only in late stages when dire complications have occurred. Europe is not spared by this scourge, with its estimated 19,000,000 persons infected, and knowledge of the epidemiology of HCV and its drivers is a critical tool in fighting this virus. A thorough review is provided on the extent of the HCV epidemic across Europe, with a discussion of the most important subgroups affected, and of the risk factors of infection, both traditional and new.

1. Introduction

The hepatitis C virus (HCV) is a major global pathogen, and its related public health burden is expected to increase further in the next few years [1,2]. According to some estimates, 3–4 million people are newly infected every year worldwide, and 350,000 patients die every year due to HCV-related disorders [3]. The toll of HCV infection is essentially due to its long term hepatic and extrahepatic consequences [4,5] The limited effectiveness of treatments available until a couple of years ago have led HCV-associated mortality to exceed that due to the human immunodeficiency virus (HIV) in developed countries, where potent drugs exist to manage HIV [6,7]. It must be added that HCV is widely under documented on death certificates [8] and therefore a true appreciation of the HCV-related health burden is lacking. In addition, the clinical impact of some extrahepatic disorders, leading to renal, cardiac and cerebrovascular outcomes associated with cryoglobulinemia and diabetes, has been emphasized only recently [4,5,9,10] and traditionally neglected in cost-effectiveness analyses. Safe and effective drugs are now available, although their cost will impose prioritization in their allocation. Thus, the next challenge will consist in identifying patients at risk of increased morbidity and mortality due to HCV, to link them to proper care, and to treat them. Through mathematical modelling, it has recently been shown that continuing to treat chronic hepatitis C patients with the current uptake rate will have a minor impact on the health burden by the year 2030, when the incidence of terminal stages of liver disease will reach its peak [2]. Thus, a better knowledge of HCV epidemiology and its movers may substantially contribute to an effective control of this troubling pandemic by focusing screening strategies on people at risk of disease progression, in order to get them into proper care and earlier treatment. The scope of this review article is to provide an update on the challenges regarding the epidemiology of HCV across Europe, and to foster the discussion about such potential strategies.

2. General epidemiology of HCV in Europe

A recent study [11], covering the geographical area of Europe as defined by the WHO (i.e. including the former USSR republics) has estimated that the prevalence of HCV varies between 2.4% for Western and Central Europe and 2.9% for Eastern Europe. The global population of this area is approximately 740,000,000 persons, leading to an estimation of the HCV infected pool of more than 19,000,000 persons, a number to be adjusted in the future given the limited evidentiary support, especially for some countries in Central Europe and for the whole Eastern European bloc. The shortcomings of this and other studies reside in the fact that evidence is based on surveys often conducted in selected groups, or excluding high-risk populations such as prison inmates and groups of persons living in social exclusion. Furthermore, many studies are outdated and have failed to take into consideration the influence of some recent drivers such as migratory movements, including those regarding war refugees and illegal human trafficking. We will discuss some of these shortcomings below.

Even more patchy is the evidence concerning the disease burden, although recent studies have tried to fill the gap conducting

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intensive local surveys and expert interviews [12–14]. According to the study by Perz et al. [3], from the US Centers of Disease Control and Prevention, the attributable fractions of cirrhosis for HCV are 38% for Western and 34% for Eastern Europe [3], while those for hepatocellular carcinoma are, respectively, 44% and 15%. HCV-specific mortality is available for a few selected countries. For example, the mortality due to HCV in Spain is 11.25 per 100,000 [15] while in France there are 2.5 HCV-associated deaths per 100,000 inhabitants (95% had cirrhosis at the time of death) [16]. Concerning the disability-adjusted life years (DALYs) related to hepatitis C, the same Spanish study estimated that approximately 76,000 DALYs – calculated without applying social values – were attributed to HCV in 2006, although after the application of the discount rate and age-weighting, the burden of disease is almost halved. Nonetheless, this study underscored the fact that the overall burden of hepatitis C is the leading cause of DALYs among transmissible diseases, at least in Spain, although it is reasonable to assume similar conclusions for other major European countries. The mortality component, in the same study, represented more than 90% of the burden of hepatitis C. Overall, estimations via HCV-attributable fractions suggest that HCV causes more than 86,000 deaths and 1.2 million DALYs in the WHO European region [17]. Finally, about one-quarter of liver transplantations performed in 25 European countries in 2004 were attributable to HCV [17].

Although these figures are already compelling, recent modelization has estimated how these numbers will increase in the next decades [2]. The disease progression model took into account the historical number of HCV infections, the age and gender distribution, the extent and impact of the movers of the HCV viraemic pool (i.e. so-called inputs and outputs, encompassing acute infections progressing to chronicity, migration movements, treatment uptake succeeding into viral eradication and deaths), the progression rates (based on literature data) and the all-cause mortality data gathered from the Human Mortality Database [18] adjusted for incremental increases due to drug abuse and blood transfusion. This model was applied to several major European countries, including Austria, Belgium, the Czech Republic, Denmark, England, France, Germany, Portugal, Spain, Sweden and Switzerland [2] (Table 1). Accordingly, the number of decompensated cirrhosis cases of HCC and the liver-related mortality will increase by 55–110%, 10–140% and 1–130%, respectively, across the period 2013–2030, with only one exception represented by France, where these figures will decrease by 80%, 85% and 75%, due to the fact that the use of more potent antivirals will be implemented via an aggressive treatment uptake.

The diagnosis rate is clearly a major hurdle to implement strategies to reduce the future health burden of HCV. As shown recently [2], countries with a centralized registry, such as Austria, Denmark, France, Germany, Sweden and Switzerland, tend to boast the highest diagnosis rates (i.e. up to 80% for Sweden), while the lowest rates were reported for Portugal (33%). Virtually everywhere screening strategies have been dictated by identification of patients with a history of exposure via the traditional routes. However, screening strategies based on risk factors have traditionally failed to identify all patients at risk of infection, leaving a sizable proportion of patients unaware of their infection. The diagnosis rate varies across European countries between 31% in the Czech Republic and 81% for Sweden [2], indicating that strategies should be radically modified (see below).

3. Old and new drivers of the HCV epidemic: iatrogenic transmission of HCV

The relative impact of the different drivers of the HCV viraemic pool (Fig. 1) has changed over recent decades. A significant number of individuals acquired HCV in the 1970s and early 1980s, i.e.

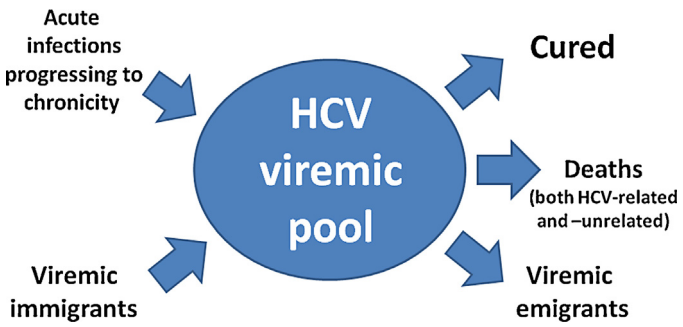

Fig. 1. Inputs and outputs of the hepatitis C viraemic pool in any given geographical area. *Abbreviations*: HCV, hepatitis C virus.

before screening assays were available and the improved awareness of blood borne pathogens – catalyzed, among others, by the AIDS scare – prompted safer medical practices. Across most of Europe, before the advent of screening assays, most infections were iatrogenic, i.e. due to transfusions with infected blood and its derivatives or to unsafe invasive medical and surgical procedures. Although before 1990 the risk of transmitting HCV via *blood transfusions* was significant (0.45% per unit transfused) [19], the introduction of screening assays reduced this risk to less than 1 per 1,000,000 units of blood [20], and the transmission of HCV via other blood products and even organ transplantation has been reduced to zero. Similarly, the prevalence of HCV in haemophiliacs has been traditionally very high [21], but after the introduction of recombinant clotting factors new cases of HCV in haemophiliacs have become exceptional [22]. On the other hand, HCV transmission has been consistently documented through use of blood-contaminated objects. A case–control study from Italy showed how the *use of non-disposable needles* within or outside the same family bore a significant risk of spreading HCV within close communities [23]. Iatrogenic transmission of HCV has since declined dramatically, and unsafe injections and medical procedures (such as wound sutures, surgical interventions and dental treatment) are still a scourge predominantly in resource-poor areas of the globe [9]. However, some small outbreaks are still reported also in Europe, due to breaches in standard safety procedures, suggesting insufficient awareness among health care providers, such as the case in a carefully documented series of patients having undergone sclerotherapy of varicose veins in France [24]. Similarly, an interesting case–control study on 450 HCV seropositive persons conducted in France [25] identified several unconventional risk factors for transmission of HCV and possibly other blood borne agents. Routes at risk of transmitting HCV included not only nosocomial admissions, but also digestive endoscopy, abortions, skin ulcer and wound cares, diathermy, injections, varicose vein sclerotherapy, acupuncture, practice of contact sports, beauty treatments and professional pedicure/manicure [25].

A strict adherence to standard precautions is obviously mandatory to prevent nosocomial HCV transmission, and this is the case for *digestive endoscopy* and *invasive radiology procedures*, as shown by studies conducted in Spain [26–28] and France [25,29] in recent years. Nevertheless, according to a large prospective cohort study carried out in a tertiary referral hospital in Turin, Italy [30], all 8260 persons undergoing digestive endoscopy remained negative for anti-HCV 6 months after the procedure, and even the 912 patients who had undergone endoscopy with the same instrument previously used on HCV-infected patients failed to seroconvert to anti-HCV, suggesting that proper hygiene and infection control practices may avoid transmission of HCV. Using dedicated endoscopy devices and rooms for patients with HCV may be an excessive measure, whereas experiments conducted on endoscopes intentionally contaminated with HCV and later disinfected