and high-dependency unit (HDU).[7] In the 14 month study period, 1854 patients were sampled for *S aureus* culture at admission to the ICU or HDU, weekly thereafter, and at discharge. In parallel, 198 health-care workers and 40 near-patient environmental locations were screened at 4 week intervals. The active surveillance identified 386 (21%) of 1854 patients with nasal staphylococcal carriage at admission and 115 (58%) of 198 health-care workers who yielded positive culture for *S aureus*, including 36 (19%) who were persistent carriers. Whole-genome sequencing results showed that most isolates had high genetic diversity. Notably, of 97 patient acquisitions of *S aureus* observed during the study, only 25 transmissions (ie, with pairs of isolates differing by no more than 40 single-nucleotide variants)—seven from health-care workers, two from the environment, and 16 from other patients—were identified .

The study had some limitations. First, data for some important risk factors for *S aureus* acquisition—including antibiotic use, hand hygiene compliance, and *S aureus* colonisation pressure over time—were not available.[8] Second, the 4 week interval between screening of health-care workers could underestimate the role of transient carriage in transmission of *S aureus* from health-care workers to patients. Nevertheless, this study highlights the complexity of *S aureus* dynamic in ICUs with standard infection control measures. The authors showed the limited role of the environment and health-care workers in transmission of *S aureus* to patients. These results reinforce previous findings that, in most cases, endogenous staphylococcal colonisation causes subsequent infections, particularly in some groups such as patients with impaired skin barriers.[9,10] Therefore, strategies based on elimination of nasal carriage represent an effective strategy to reduce the incidence of *S aureus* infections.[6,9]

However, we should keep in mind that Price and colleagues' study was done in a non-epidemic context with a low prevalence of MRSA. The use of whole-genome sequencing, with its high discriminatory power, will allow us to better understand the different route of transmission of important human pathogens such as *S aureus*.[11,12] Further investigations compiling epidemiological and genetic data are essential to determine the multiple sources of transmission and to assess the effectiveness of strategies for prevention of nosocomial infections.

Olivier Denis
National Reference Centre for *Staphylococcus aureus*, Hôpital Erasme, and Ecole de Santé Publique, Université Libre de Bruxelles, Route de Lennik 808, 1070, Brussels, Belgium
odenis@ulb.ac.be

I declare no competing interests.

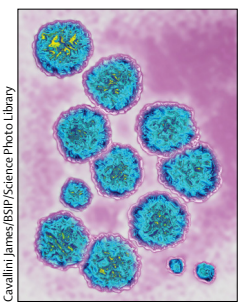
1 Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302:** 2323–29.
2 Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol* 2016; **37:** 1288–1301.
3 de Kraker ME, Jarlier V, Monen JC, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. *Clin Microbiol Infect* 2013; **19:** 860–68.
4 Mulcahy ME, McLoughlin RM. Host–bacterial crosstalk determines *Staphylococcus aureus* nasal colonization. *Trends Microbiol* 2016; **24:** 872–86.
5 Van Belkum A, Verkaik NJ, de Vogel CP, et al. Reclassification of *Staphylococcus aureus* nasal carriage types. *J Infect Dis* 2009; **199:** 1820–26.
6 Simor AE. Staphylococcal decolonisation: an effective strategy for prevention of infection? *Lancet Infect Dis* 2011; **11:** 952–62.
7 Price JR, Cole K, Bexley A, et al. Transmission of *Staphylococcus aureus* between health-care workers, the environment, and patient in an intensive care unit: a longitudinal cohort study based on whole-genome sequencing. *Lancet Infect Dis* 2016; published online Nov 15. http://dx.doi.org/10.1016/S1473-3099(16)30413-3
8 Bloemendaal AL, Fluit AC, Jansen WM, et al. Acquisition and cross-transmission of *Staphylococcus aureus* in European intensive care units. *Infect Control Hosp Epidemiol* 2009; **30:** 117–24.
9 Kalmeijer MD, Coertjens H, van Nieuwland-Bollen PM, et al. Surgical site infections in orthopedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study. *Clin Infect Dis* 2002; **35:** 353–58.
10 Von Eiff C, Beker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. *N Engl J Med* 2001; **344:** 11–16.
11 Köser CU, Holden MT, Ellington MJ, et al. Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. *N Engl J Med* 2012; **366:** 2267–75.
12 Roisin S, Gaudin C, De Mendonça R, et al. Pan-genome multilocus sequence typing and outbreak-specific reference-based single nucleotide polymorphism analysis to resolve two concurrent *Staphylococcus aureus* outbreaks in neonatal services. *Clin Microbiol Infect* 2016; **22:** 520–26.

Cutting out the roots of acute hepatitis C

Hepatitis C infection is mainly a chronic liver disease with severe complications such as decompensated cirrhosis and liver cancer. Several studies have shown that the consequences of chronic hepatitis C virus (HCV) infection are not confined to the liver but also increase the risk of cardiovascular and renal diseases and cancer.[1] Most patients with chronic hepatitis C were infected before 1990, when the HCV antibody testing

Published Online
October 28, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30406-6

See Articles page 215


Cavallini James/BSIP/Science Photo Library

of blood donors was introduced. The incidence of acute hepatitis C has fallen substantially because of improvements in hospital hygiene and aseptic conditions during invasive medical and surgical techniques, and because of the very low risk of contamination through blood transfusion, at least in high-income countries (<1 per 2 million blood units).[2] There nevertheless remains a risk of acute hepatitis, particularly among people who inject drugs, HIV-positive and HIV-negative men who have sex with men, and more rarely in health-care workers, as well as in countries where blood donations are not secure regarding the transmission of HCV infection or where hospital hygiene is suboptimal.

By contrast with acute HIV infection, there are no guidelines for the preventive treatment of patients at risk of acute HCV infection but without documented acute HCV hepatitis. However, the treatment of early HCV during the acute phase is crucial to preventing chronicity and long-term complications. The treatment of acute hepatitis C can be difficult. Mostly asymptomatic, the disease usually goes undiagnosed and is only detected when screening is done in a population at risk or when the disease becomes symptomatic. The risk of evolution from acute to chronic infection is high (50–80%), but not constant, so any decision to treat acute hepatitis or not must be balanced; this was notably the case in the early years of interferon use because this drug was poorly tolerated. In 2001, a study showed that interferon-based therapy was highly effective if initiated less than 3 months after the onset of infection,[3] but its potential adverse effects led to many patients refusing the drug.

In *The Lancet Infectious Diseases*, Katja Deterding and colleagues[4] report the first prospective study investigating the efficacy and safety of a 6-week course of ledipasvir plus sofosbuvir for treatment of acute HCV genotype 1 monoinfection. Such a study was eagerly awaited. 20 patients, recruited from ten centres in Germany, were treated, and all achieved a sustained virological response 12 weeks after completion of study treatment. This result might have been predicted in view of the efficacy of all-oral interferon-free regimens to treat chronic hepatitis C, even in patients with advanced liver disease.[5] The findings support the preliminary data of the SLAM C study in which 29 people who inject drugs and had acute HCV genotype 1 infection were treated with sofosbuvir and ledipasvir (14 patients) for 4 weeks, or sofosbuvir and simeprevir (15 patients) for 8 weeks. In a per-protocol analysis, the proportion of patients who achieved a sustained virological response was 100% in both groups.[6]

Another important factor highlighted by the study by Deterding and colleagues is the duration of treatment. If hepatitis C is treated early, before the occurrence of underlying liver fibrosis, this will facilitate viral clearance and enable a shorter treatment duration, which at present is between 8 and 12 weeks for patients with chronic hepatitis C.[6] A 6-week course seems to be sufficient to treat acute HCV genotype 1 monoinfection using the combination of ledipasvir and sofosbuvir. However, in the absence of data, no recommendations can be made for other combinations of direct-acting antiviral agents. During the DARE-C study, 19 patients (including 14 with HIV co-infection) were treated for acute hepatitis C with sofosbuvir and ribavirin for 6 weeks, and the proportion of patients who achieved a sustained virological response only reached 32%.[7] Treatment combining sofosbuvir and ribavirin could not be recommended. In the SWIFT-C study, 17 HIV-infected patients were treated for acute hepatitis C with a combination of sofosbuvir and ribavirin for 12 weeks, and 59% of patients achieved a sustained virological response.[8] Finally, no data have as yet been published on patients with an acute infection of HCV genotype 3.

The good tolerability of interferon-free combination therapies is an argument in favour of their use to treat acute hepatitis C. Deterding and colleagues reported only one serious adverse events with ledipasvir plus sofosbuvir, which was deemed unrelated to treatment, although 22 potentially treatment-related events occurred, the most frequent being gastrointestinal symptoms in four patients.

The most important effect of treating acute hepatitis C is the reduction of the spread of this disease, which is difficult to demonstrate. This approach is crucial to preventing the appearance of new cases, and forms part of efforts to achieve eradication of the virus through the universal treatment of hepatitis C. However, to be effective, this approach must be accompanied by a comprehensive care package that includes routine screening in high-risk populations, preventive measures, and health education. Indeed, it is important that patients should be aware of how HCV infection can be transmitted and implement behaviour to avoid any recontamination.[9] The role of patient

organisations and structures that support people who inject drugs and at-risk individuals is particularly important in this situation.

Potential limitations of the study by Deterding and colleagues include the small number of patients and the high rates of re-infection in at-risk populations receiving high-cost treatment. However, other studies will be done to establish the optimum strategy, and the costs of treatment will subsequently fall. Finally, most patients with acute HCV infection in high-risk populations will be treated, so that the number of patients able to transmit HCV will decrease as a result, although this should not obviate the importance of preventive measures.

*Audrey Coilly, *Didier Samuel*
AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif F-94800, France; Université Paris-Sud, UMR-S 1193, Université Paris-Saclay, Villejuif, France; Inserm, Unité 1193, Université Paris-Saclay, Villejuif, France; and Hepatinov, Villejuif, France
didier.samuel@aphp.fr

AC reports consultancy fees and payment for lectures from Novartis, Roche, Astellas, Bristol-Myers Squibb, Gilead, Janssen, and Merck Sharp & Dohme. DS reports consultancy for lectures from Astellas, Gilead, Bristol-Myers Squibb, LFB, MSD, Novartis, Roche, Biotest, and Abbvie.

1 Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology* 2015; **149:** 1345–60.
2 Pillonel J, Brouard C, Laperche S, et al, for the Groupe de Travail Afssaps, EFS, INTS et InVS. Quantitative estimate of the risk of blood donation contamination by infectious agents. *Transfus Clin Biol* 2009; **16:** 138–45 (in French).
3 Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345:** 1452–57.
4 Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Lancet Infect Dis* 2016; published online Oct 28. http://dx.doi.org/10.1016/S1473-3099(16)30408-X.
5 Felmlee DJ, Coilly A, Chung RT, Samuel D, Baumert TF. New perspectives for preventing hepatitis C virus liver graft infection. *Lancet Infect Dis* 2016; **16:** 735–45.
6 Basu P, Shah NJ, John N, Aloysius M, Brown R. Sofosbuvir and ledipasvir versus sofosbuvir and simeprevir combination therapy in the management of acute hepatitis C: a randomized open label prospective clinical pilot study. SLAM C study. Interim data. *Hepatology* 2015; **62** (suppl 1)**:** 736A.
7 Martinello M, Gane E, Hellard M, et al. Sofosbuvir and ribavirin for six weeks is not effective among people with acute and recently acquired HCV infection: the DARE-C II study. *Hepatology* 2015; **62** (suppl 1)**:** 741A.
8 Naggie S, Marks KM, Hughes M, et al. Sofosbuvir plus ribavirin without interferon for treatment of acute hepatitis C virus infection in HIV-1 infected individuals (SWIFT-C). *Hepatology* 2015; **62** (suppl 1)**:** 748A.
9 Grebely J, Prins M, Hellard M, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. *Lancet Infect Dis* 2012; **12:** 408–14.

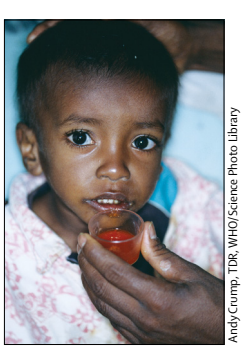
Time to review treatment of isoniazid-resistant tuberculosis?

Despite substantial investment over many years, tuberculosis is still a global threat.[1] The main focus at present is containment of the spread of multidrug-resistant and extensively drug-resistant tuberculosis, but the Article[2] by Medea Gegia and colleagues in *The Lancet Infectious Diseases* is a reminder that even mono-resistance to isoniazid needs to be managed with care. To assume that standard first-line drugs will cure these cases can be dangerous.

The 2014 reported global rate of isoniazid resistance not associated with rifampicin resistance was 9·5%,[1] and the estimated prevalence of multidrug-resistant tuberculosis was 4·8%. Thus almost twice as many people with tuberculosis harbour isoniazid-resistant strains (either resistant to isoniazid only or coupled with resistance to another first-line drug) as harbour multidrug-resistant strains.[1,2] Because standard first-line regimens are the recommended treatment of tuberculosis resistant to isoniazid only, less attention and scientific interest has been paid by clinicians and public health experts, who are focused on the complexities of treating multidrug-resistant and extensively drug-resistant disease.[3,4]

A systematic review[3,4] of treatment outcomes of more than 9000 patients with multidrug-resistant or extensively drug-resistant disease showed that the median treatment success rate was 62% (64% in multidrug resistance and 40% in extensive drug resistance). The success rate in tuberculosis with a drug-resistance profile beyond extensive drug resistance was lower than 20%.[4] The findings of the regression analysis done in that systematic review were the basis for the 2011 WHO guidelines for management of multidrug-resistant tuberculosis management.

So far, treatment outcomes in patients with mono-drug-resistant or poly-drug-resistant cases have not been so thoroughly investigated, although concerns about suboptimal results were raised by the authors of one study.[5] The comprehensive meta-analysis[2] of treatment outcomes in patients with isoniazid-resistant, rifampicin-sensitive tuberculosis by Gegia and colleagues is therefore timely and important. The


Andy Crump, TDR, WHO/Science Photo Library

Published **Online**
November 16, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30381-4

See **Articles** page 223