

“Body Packers” in Israel: A Case Series

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ABSTRACT: **Background:** “Body packers” swallow multiple packets filled with illicit drugs, mainly cocaine, in order to smuggle them across international borders. In recent years, an increasing number of body packers have been hospitalized after their detention by the police upon arrival in Israel.

Objectives: To characterize the clinical features and outcomes of body packers hospitalized at the Sheba Medical Center.

Methods: We conducted a retrospective case series of body packers hospitalized between January 2010 and October 2012 in our medical center. Electronic medical records and imaging files were reviewed to extract clinical, laboratory and radiological data as well as details on medical treatments.

Results: We identified 23 body packers (mean age 38 ± 10 years), 20 of whom smuggled cocaine from South America. The number of packets transported ranged from 1 to 242 (median 42) and duration of hospitalization from 1 to 14 days (median 2). Two subjects required surgical intervention. All others were treated conservatively by polyethylene glycol-electrolyte lavage solution, laxatives, or watchful waiting. Ten patients underwent a urinary screen for illicit drugs, 7 of whom tested positive for cocaine and 2 for cannabinoids. Abdominal X-rays were performed in all patients at admission, and 14 had follow-up imaging, including abdominal CT scans without contrast media in 8.

Conclusions: The main treatment goals for body packers are the rapid excretion of drug packets and early detection of complications, i.e., drug intoxication and bowel obstruction. We suggest the use of a structured treatment approach for the in-hospital management of body packers.

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KEY WORDS: body packers, drug mules, cocaine

range of specialists in Israel, including emergency physicians, internists, surgeons, radiologists, and clinical toxicologists. Only four cases of body packers have been reported from Israel during the last two decades [1-4], and most physicians are still unfamiliar with this specific patient population and its diagnostic and therapeutic challenges. Given the increasing number of body packers detained upon arrival in Israel, the objective of this study was to characterize the typical body packer based on a series of 23 body packers recently hospitalized in our institution.

PATIENTS AND METHODS

Subjects suspected of body packing who are detained by the police upon arrival at the Ben-Gurion International Airport are brought to the emergency department of a nearby hospital, typically the Sheba Medical Center. After the suspicion is confirmed by medical examination and imaging studies in the emergency department, uncomplicated patients are either admitted to a medical ward or remain in the emergency department's short-term admission ward. The objectives of hospitalization are to achieve rapid and safe excretion of all drug packets and to observe the patient for complications, particularly drug intoxication from perforated packets or bowel obstruction from impacted packets. Throughout hospitalization, subjects are under the surveillance of police officers, who collect all excreted drug packets and perform bedside diagnostic tests to identify the type of illicit drug.

To identify body packers, we conducted a retrospective review of discharge diagnoses among foreigners hospitalized in the Sheba Medical Center medical wards between January 2010 and October 2012. In addition, we reviewed the toxicological consultations provided to hospitalized patients by clinical toxicologists. After identifying a body packer, we reviewed the electronic medical records to extract demographic and clinical data, laboratory results (including urinary screen for drugs of abuse), details on type of drug, wrapping technique, and number of packets swallowed, as well as information on therapeutic interventions (e.g., use of bowel irrigation or laxatives). In addition, we reviewed all abdominal X-rays and computed tomography scans performed at admission and during hospitalization.

“Body packers,” also known as “drug mules,” swallow dozens of small packets filled with illicit drugs, mainly cocaine, in order to smuggle them across international borders. A long-known phenomenon in Europe and the United States, these “travelers” present a new and growing challenge for a wide

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RESULTS

We identified 23 body packers (aged 38 ± 10 years, range 24–64 years, 13 males) [Table 1], 20 of whom arrived from South America smuggling cocaine, and 2 from India via Jordan smuggling cannabis (the type of drug was not listed in the medical record of one patient arriving from South America). Except for three, all were foreign nationals, usually from their respective country of departure. Body packers were often detained in groups of two to three unrelated subjects (co-smugglers) who had received identical drug packets from the same dispatcher.

IN THE EMERGENCY DEPARTMENT

A diagnosis of body packing was made based on direct identification of drug packets (excreted in the feces of 7 subjects and detected by rectal examination in 2 others) or on informative abdominal imaging (14 subjects). On admission, 15 patients displayed abnormal physical or laboratory findings: 6 were hypertensive ($\leq 195/109$ mmHg), 8 displayed sinus tachycardia (≤ 148 beats/min), 6 had leukocytosis ($\leq 19,000/\mu\text{l}$), and 4 had mild abdominal tenderness upon physical examination.

INITIAL IMAGING STUDIES

Supine abdominal X-rays were performed in all subjects in the emergency department, eight of whom demonstrated classic radiological findings of multiple, round, homogenous opacities rimmed by a thin radiolucent ring (“double condom” sign, discussed below). In contrast, abdominal X-ray imaging was not diagnostic in 15 patients, displaying only vaguely defined opacities that could be misdiagnosed as normal bowel contents. Four of those patients had an abdominal CT scan without contrast media, which confirmed the diagnosis of ingested packets. Although most X-rays displayed mild distension of the colon, none showed signs of intestinal obstruction or perforation.

DRUG PACKETS

The number of packets retrieved varied from 1 to 242 (median 42). Eight patients reported the number of ingested packets, which was highly concordant with the number of packets excreted (mean difference < 1 packet). Fifteen patients did not know or were unwilling to report the number of packets ingested. Cocaine was smuggled as powder (13 cases) or liquid (7 cases), commonly wrapped in multiple layers of latex, measuring about 2×3 cm. Cannabis was wrapped in clinging plastic. Except for a few packets removed surgically in one patient, there were no reports of disintegration of packet wrappings after inspection of excreted drug packets by the attending police officers.

URINARY SCREEN FOR ILLICIT DRUGS

Nine subjects were screened for drugs of abuse in the urine (Enzyme Immunoassay, Microgenics Corporation, CA, USA) during the first few hours of hospitalization: six tested posi-

tive for cocaine, two tested positive for cannabinoids, and one tested negative. A tenth patient tested positive for cocaine on the fourth and fifth days of hospitalization, with no reference test from admission. The patient was monitored for another 24 hours, during which there were no signs and symptoms of systemic intoxication, and an abdominal CT scan confirmed complete evacuation. Among seven subjects testing positive for cocaine metabolites, only two had signs compatible with cocaine exposure (tachycardia and hypertension).

CLINICAL COURSE

The median duration of hospitalization was 2 days (range 1–14). Most body packers ($n=19$) had an uneventful course. Ten of the 19 consented to treatment with polyethylene glycol-electrolyte lavage solution or a laxative (such as lactulose or paraffin), and no additional pharmacological interventions were required. A young female body packer who reported a recent spontaneous abortion followed by persistent vaginal bleeding was diagnosed with incomplete abortion and underwent dilatation and curettage.

DISCHARGE CRITERIA FOR UNCOMPLICATED PATIENTS

Patients with an uncomplicated clinical course ($n=19$) were considered for discharge if two consecutive packet-free bowel movements had been passed ($n=9$), follow-up abdominal imaging demonstrated complete clearance of packets ($n=4$), or if both of the above criteria were fulfilled ($n=5$). Another patient was discharged after passing the number of packets that he reported having swallowed.

PATIENTS WITH A COMPLICATED CLINICAL COURSE

Four subjects suffered complications. One patient developed left lower quadrant pain and tenderness and scant rectal bleeding, without physical signs of peritonitis. Abdominal X-ray suggested neither foreign bodies nor signs of obstruction or perforation, but a CT scan demonstrated two remaining packets in the ascending colon. The patient passed both remaining capsules during the next few hours, all symptoms subsided, and she was discharged the following day.

A second patient had swallowed an unknown number of drug packets. Abdominal X-ray on the third day suggested complete clearance, but she continued passing packets in the stool. On the eighth day, after having passed 48 drug packets, she became restless and complained of diffuse abdominal pain. Physical examination revealed mild diffuse abdominal tenderness, and a CT scan demonstrated two remaining packets in the transverse colon, with no signs of obstruction or perforation. Laboratory tests showed no abnormalities, and her urine tested negative for cocaine metabolites, similar to the drug screen upon admission. During the next few hours, the two packets identified on CT were passed in the stool, her symptoms resolved completely and she was subsequently discharged.

Table 1. Demographic and clinical variables

Age/ Gender	Origin	Drug type/ no. of packets	Hosp length (days)	Clinical course	Urine screen	Emerg department X-ray	Discharge criteria	Laxative
25 / M	SA	Liquefied cocaine/?	1	Uneventful	Not performed	Non-diagnostic	Negative X-ray	None
43 / F	SA	Cocaine/ 35	1	Abdominal pain	Not performed	Positive	Negative X-ray	None
64 / M	SA	Liquefied cocaine/ 60	2	Tachycardia, HTN, leukocytosis	Not performed	Non-diagnostic	Negative CT	PEG
44 / F	SA	Cocaine/125	2	Uneventful	Not performed	Positive	Negative X-ray + 2 clean stools	PEG
44 / M	SA	Cocaine capsules/100	2	Abdominal pain, migraine	Not performed	Positive	Negative X-ray + 2 clean stools	PEG + paraffin
37 / F	SA	Cocaine capsules/?	5	Abdominal pain, rectal bleeding	Not performed	Positive	Negative CT	PEG + paraffin
34 / M	SA	Liquefied cocaine/?	1	Uneventful	+	Non-diagnostic	2 clean stools	None
41 / F	S.A.	Cocaine/?	2	Uneventful	+	Non-diagnostic, confirmed by CT	2 clean stools	None
35 / M	India	Hashish/242	3	Uneventful	+	Positive	Negative x-ray + 2 clean stools	PEG
35 / M	India	Hashish/113	3	Uneventful	+	Positive	2 clean stools	PEG
32 / M	SA	Liquefied cocaine/50	2	Tachycardia, HTN	Not performed	Non-diagnostic	Negative X-ray	None
41 / F	SA	Cocaine/?	4	Uneventful	Not performed	Non-diagnostic	2 clean stools	Lactulose
42 / M	SA	Cocaine/30	1	Tachycardia	Not performed	Non-diagnostic	2 clean stools	None
25 / F	SA	Cocaine/?	1	Tachycardia, HTN	Not performed	Non-diagnostic	2 clean stools	None
53 / M	SA	Cocaine/20	1	HTN	Not performed	Non-diagnostic	Passing of self- reported no. of packets	None
44 / F	SA	Liquefied cocaine/38	2	Leukocytosis	+	Positive	2 clean stools	Lactulose
26 / F	SA	Cocaine/50	9	Abdominal pain	Negative	Positive	Negative CT + 2 clean stools	Paraffin
37 / M	SA	Cocaine/42	14	Laparotomy	+	Non-diagnostic, confirmed by CT	Negative CT	Lactulose
24 / F	SA	Liquefied cocaine/38	6	D/C for retained placenta, tachycardia	+	Non-diagnostic	2 clean stools	Lactulose
45 / F	SA	Cocaine capsules/43	5	Abdominal pain, leukocytosis	+	Non-diagnostic	2 clean stools	Lactulose
26 / M	SA	Liquefied cocaine/31	3	Tachycardia	Not performed	Non-diagnostic, confirmed by CT (low radiation protocol)	Negative CT + 2 clean stools	None
31 / M	SA	Cocaine/23	6	Leukocytosis	+	Non-diagnostic	Suggestive CT + 1 clean stool	None
44 / M	SA	?†/1	10	Abdominal pain, HTN, leukocytosis	Not performed	Non-diagnostic, confirmed by CT	Packet removal by laparoscopy	None

†The packet was confiscated by the police without performing bedside diagnostic tests
SA = South America, HTN = hypertension, PEG = polyethylene glycol-electrolyte lavage solution

The third patient, a 34 year old male, was detained at the airport after exhibiting anxiety and profuse sweating during the flight from South America. He reported swallowing 100 packets of cocaine and admitted to heavy recreational use of both cocaine and other unidentified illicit drugs before boarding the plane. On admission, his blood pressure was 184/103 mmHg, heart rate was 124 bpm and oral temperature 37.9°C. Abdominal CT demonstrated packets throughout the

gut without signs of obstruction. Three intact latex-wrapped packets containing cocaine were retrieved from the rectum by a surgeon. The next day, the abdomen was distended and was accompanied by leukocytosis (20,000/μl), hyperlactatemia (60 mg/dl), and non-specific electrocardiographic changes. Urgent laparotomy for suspected bowel obstruction disclosed 39 packets, which were removed through a single gastric incision and through the rectum by “milking” them

along the bowel. Three packets had air trapped between layers of latex, and an additional packet was partially torn. The postoperative period was complicated by paralytic ileus, aspiration pneumonia, and symptoms of cocaine withdrawal, requiring the use of opiates for sedation. He was discharged after 14 days and a follow-up examination revealed an uneventful recovery.

The fourth patient presented with a single large radio-opaque foreign body in the antral portion of the stomach. This finding was not identified on initial abdominal and chest X-rays but was visualized on subsequent abdominal CT. Since two follow-up CT scans did not demonstrate progression of the packet over a period of 5 days, abdominal laparoscopy was performed on the 6th day of hospitalization. A large (2.5 x 5.5 cm) cylindrical capsule wrapped in nylon was retrieved and confiscated by police officers. He had an uneventful recovery and was discharged 4 days after surgery.

DISCUSSION

This case series shows that the demographic characteristics and clinical course of body packers hospitalized in Israel are comparable to those described in European and North American series. Most body packers detained in Israel smuggled cocaine from South America and had an uneventful clinical course. However, treatment approaches varied substantially among the 23 patients, due in part to the lack of a unified treatment protocol.

The first case of body packing was reported in Canada in 1973, when a young man presented with bowel obstruction after swallowing a single condom filled with hashish [5]. Since then, various types of smuggled drugs and wrapping techniques have evolved and body packing has become a common phenomenon in large airports. The typical body packer is a young to middle-aged male or female foreigner of low socioeconomic status, usually a national of the country of departure, with no or only occasional self-use of illicit drugs, who consents to body packing as a means of escaping poverty. Cocaine is the most common drug identified

(70%–90%), followed by heroin [6]. Other substances are rarely found, mainly due to low profit margins in the illegal drug market. In Israel, most detained body packers arrive from South America carrying cocaine. Others may bypass the airport, crossing the land borders from Egypt, Jordan or Lebanon, carrying cocaine and hashish.

The total amount of cocaine smuggled by a single body packer may reach 1 kg, divided into dozens or hundreds of small packets weighing 2–15 g each. In the country of origin, body packers go through a vigorous preparatory ritual, including whole-bowel irrigation, followed by the swallowing of packets with the aid of a sedative, and then anti-motility agents throughout the journey. At the destination, pro-motility agents enhance evacuation. Since many body packers are naive to cocaine, rupture of as little as one packet within the gut may result in lethal toxicity [7]. Aside from being swallowed, packets may also be hidden in body cavities, such as the rectum or vagina, a practice referred to as “body pushing.” By contrast, subjects who hastily swallow drug packets to conceal incriminating evidence when surprised by police officers are termed “body stuffers.” Such drug packets are usually poorly manufactured and entail a high risk for rupture within the gastrointestinal tract [8].

WRAPPING

In the past, drugs were amateurishly wrapped in aluminum foil, making packets radio-opaque and thus easy to detect but also prone to rupture within the intestinal tract, exposing the body packer to systemic toxicity and death. Subsequently, condoms and unilayer latex gloves were used, resulting in less toxicity as well as reduced detectability on abdominal X-rays since these materials are relatively radiolucent [7]. Today, especially in South America, machine-made capsules or multilayered latex wrappings are used [Figure 1], making rupture extremely rare but potentially increasing the risk of bowel obstruction as body packers feel confident to swallow a larger number of packets. Additionally, cocaine is used increasingly in its liquid form, since it is more difficult to detect on plain abdominal imaging compared to powder.

Figure 1. Packets retrieved from body-packers hospitalized at the Sheba Medical Center. **[A]** Hashish wrapped in clinging plastic wrapping. **[B]** Encapsulated cocaine. **[C]** Liquefied cocaine wrapped in latex



Figure 2. Abdominal imaging of body-packers hospitalized at the Sheba Medical Center. **[A]** Uniform capsules forming the typical “tic-tac” sign. **[B]** Drug packets that can be misdiagnosed as normal bowel content. **[C]** “Double condom” sign – packets are rimmed by a thin, radiolucent line. **[D]** Abdominal CT, viewed in lung window, demonstrating two distinct drug packets



DETECTION ON IMAGING

Supine abdominal X-ray is the initial modality of choice for confirming the presence of packets in the gastrointestinal tract [9], with a reported sensitivity and specificity of 60% and 85%, respectively [6]. Classically, uniform rectangular opacities are arrayed throughout the gut, forming the typical “tic-tac” sign [Figure 2A]. However, especially with isodense drugs and radiolucent wrappings, packets may appear as vaguely demarcated intestinal content, resembling stool [Figure 2B] [10]. When air is trapped between two layers of latex, a thin radiolucent rim is visible around the packet, also known as the “double condom sign” [Figure 2C]. Air trapping usually occurs prior to swallowing, at the stage of drug packing, but may also be a warning sign of partial dissolution of the wrapping with impending rupture [9]. When supine abdominal X-ray imaging is inconclusive and high clinical suspicion persists, abdominal CT without intravenous or oral contrast is the gold standard for the diagnosis of body packing, with reported sensitivity and specificity approaching 100% [6]. Low radiation protocols have been suggested to be sufficiently sensitive [11], although to date there is limited published evidence. Foreign bodies are best identified using the CT lung window rather than the abdominal window [Figure 2D] [6]. Unlike plain films, CT scans usually enable exact quantification of packets. However, in view of the increased cost and radiation exposure, this imaging modality should be performed only if abdominal X-rays are inconclusive, or if bowel obstruction is suspected.

ENHANCED EVACUATION

Body packers may not be willing to comply with diagnostic or therapeutic procedures aimed at shortening their hospitalization, after which they are transferred to prison facilities. Polyethylene glycol-electrolyte lavage solution is

routinely used for bowel cleansing in asymptomatic body packers [12,13]. Dose rates of 1–2 L/hour are generally recommended, as used in aggressive whole-bowel irrigation for other toxins [14]. However, such doses usually require the placement of a nasogastric tube and are impractical in non-consenting patients. Thus, oral PEG-ELS has been used at lower dose rates and continued until all packets have passed [13]. Alternatively, laxatives and other bowel cleansers, such as lactulose, paraffin oil, or sodium picosulfate, have been used [13,15–17]. In vitro dissolution studies suggested that paraffin oil enhances latex disintegration within the digestive tract, and although this has not been clinically proven many authorities advise against its use in body packers [14]. Laxatives or bowel irrigation are contraindicated if packet rupture or bowel obstruction is suspected [5]. In these cases, emergency laparotomy is the only treatment option.

In the past, oral activated charcoal was recommended for routine gastrointestinal decontamination [14], but it does not sufficiently prevent drug absorption in case of packet rupture and greatly complicates laparotomy. Thus, activated charcoal should not be administered to body packers. In addition, endoscopic removal of packets carries the risk of rupture in the gastrointestinal tract and should be avoided [14].

URINARY DRUG SCREENING

The elimination half-life of cocaine and its primary metabolite, benzoylecgonine, is 0.5–1 hour and 5–8 hours, respectively. Therefore, benzoylecgonine can usually be detected in urine samples for up to 2–3 days following a single exposure. Approximately 50% of asymptomatic cocaine body packers have a positive cocaine urine screen on admission, reflecting either drug abuse by the smuggler or contamination

PEG-ELS = polyethylene glycol-electrolyte lavage solution

of the packets' outer layer during the wrapping process. Hospitalized body packers are under continuous police observation and therefore prevented from using illicit drugs. Thus, urine samples that become positive after an initial negative result or remain positive for 4 consecutive days or longer may indicate package leakage or rupture [18].

COMPLICATIONS: DRUG INTOXICATION AND BOWEL OBSTRUCTION

With improved wrapping techniques, the vast majority of body packers will remain asymptomatic [7], and less than 5% will develop signs and symptoms of intestinal obstruction or drug toxicity. In some large international airports, asymptomatic body packers are observed in designated facilities within the airport, equipped with X-ray machines and medical personnel, until complete evacuation. Thus, among 1250 confirmed body packers referred to a New York City hospital during the period 1993–2005, only 4.5% were eventually admitted and only 2% required surgical intervention [12].

Cocaine intoxication should be suspected if the patient becomes agitated and diaphoretic, develops chest pain or seizures, or presents with abnormal signs such as tachycardia, hypertension, fever and mydriasis. The ECG may show signs of acute myocardial ischemia. In contrast, opioid toxicity is characterized by depressed mental status, bradypnea, hypotension, myosis, and decreased bowel movement sounds. Risk factors for packet rupture or leakage include homemade wrappings, prolonged gastrointestinal transit time, and drug intoxication of a co-smuggler who carried packets from the same batch. A persistently positive urine drug test or a positive test following a previous negative one, as well as fragments of wrappings in stool, may be indicators of package rupture. Abdominal pain and tenderness, bloating, vomiting, and constipation may signal bowel obstruction. Risk factors for obstruction are previous abdominal surgery and large packet number (> 50) and/or size [15].

SURGICAL TECHNIQUES

As stated, the need for surgical intervention is currently rare. During the years 1997–2005, 1181 confirmed body packers were hospitalized in a Paris hospital, and less than 2% required surgery [17]. Patients who require surgery typically have a protracted clinical course. The average duration of hospitalization for five body packers managed surgically in a London hospital during the period 2000–2005 was 10.4 days, as compared to 2.8 days for those managed conservatively [13]. The main indications for emergency surgical intervention are suspected packet rupture and bowel obstruction. Prolonged packet retention is another indication for surgical intervention [12,17], as these packets are more likely to disintegrate or cause bowel obstruction. If laparotomy is indicated for bowel obstruction or retained drug packets, "milking" of packets towards a single incision combined with anal expul-

sion is recommended. This technique significantly reduces postoperative complications, such as infection or anastomosis leak. If, however, packet rupture is visualized, packet removal through multiple enterotomies may be required, since milking of leaking packets can increase drug release, mucosal injury, and drug absorption [17,19].

DISCHARGE CRITERIA

Guidelines for clinical management of body packers, which include algorithms for initial evaluation, in-hospital management and discharge criteria, have been developed by a number of medical centers [12,13]. Accepted discharge criteria for body packers are two or more consecutive packet-free bowel movements, followed by the documentation of complete clearance of foreign bodies on abdominal X-ray or CT scan without contrast media.

CONCLUSIONS

Drug-smuggling body packers are increasingly admitted to hospitals in Israel, and physicians from various disciplines are facing the unique challenges that arise during their treatment. We suggest that a clinical toxicologist be consulted and a structured treatment approach be used to ensure the safe and rapid evacuation of drug packets and the early diagnosis and treatment of complications.

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Capsule

Use of oral fluconazole during pregnancy and the risk of birth defects

Case reports suggest that long-term high dose fluconazole treatment for severe fungal infections during pregnancy causes a pattern of birth defects. It is unclear whether commonly used lower doses increase the risk of specific birth defects. The majority of fluconazole-exposed pregnancies were in women who received common therapeutic doses of 150 mg (56% of pregnancies) or 300 mg (31%). Oral fluconazole exposure was not associated with an increased risk of birth defects overall: 210 birth defects among 7352 fluconazole-exposed pregnancies (prevalence, 2.86%) and 25,159 birth defects among 968,236 unexposed pregnancies (prevalence, 2.60%). The adjusted prevalence odds ratio (OR) was 1.06; 95% confidence interval (CI) 0.92–1.21. In addition, oral fluconazole exposure was not

associated with a significantly increased risk of 14 of 15 types of birth defects previously linked to azole antifungal agents: craniosynostosis, other craniofacial defects, middle-ear defects, cleft palate, cleft lip, limb defects, limb-reduction defects, polydactyly, syndactyly, diaphragmatic hernia, heart defects overall, pulmonary artery hypoplasia, ventricular septal defects, and hypoplastic left heart. A significantly increased risk of tetralogy of Fallot was observed: 7 cases in fluconazole-exposed pregnancies (prevalence 0.10%) as compared with 287 cases in unexposed pregnancies (prevalence 0.03%); adjusted prevalence OR 3.16 and 95% CI 1.49–6.71.

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Eitan Israeli

Capsule

Completion of the entire hepatitis C virus life cycle in genetically humanized mice

More than 130 million people worldwide chronically infected with hepatitis C virus (HCV) are at risk of developing severe liver disease. Antiviral treatments are only partially effective against HCV infection, and a vaccine is not available. Development of more efficient therapies has been hampered by the lack of a small animal model. Building on the observation that CD81 and occludin (OCLN) comprise the minimal set of human factors required to render mouse cells permissive to HCV entry, Dorner et al. previously showed that transient expression of these two human genes is sufficient to allow viral uptake into fully immunocompetent inbred mice. Here the authors demonstrate that transgenic mice stably expressing human CD81 and OCLN also support HCV entry, but innate and adaptive immune responses restrict HCV infection in vivo. Blunting antiviral immunity in genetically humanized mice infected with HCV results in measurable viremia over

several weeks. In mice lacking the essential cellular co-factor cyclophilin A (CypA), HCV RNA replication is markedly diminished, providing genetic evidence that this process is faithfully recapitulated. Using a cell-based fluorescent reporter activated by the NS3-4A protease we visualize HCV infection in single hepatocytes in vivo. Persistently infected mice produce de novo infectious particles, which can be inhibited with directly acting antiviral drug treatment, thereby providing evidence for the completion of the entire HCV life cycle in inbred mice. This genetically humanized mouse model opens new opportunities to dissect genetically HCV infection in vivo and provides an important preclinical platform for testing and prioritizing drug candidates and may also have utility for evaluating vaccine efficacy

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