education

FROM THE JOURNALS Edited highlights of weekly research reviews

Smear stories

Half of all cases of cervical cancer in the UK are diagnosed in women who aren't up to date in their screening. But the numbers of those turning up for screening have been falling since 2005, and covid has caused further disruption. The NHS has trialled posting DIY human papillomavirus (HPV) testing kits directly to "non responders," and the question is whether it would be a good strategy for everyone.

This study of over 31 000 women aged 30-64 years who were due for screening randomly allocated them to usual care (reminders to patients and alerts on the health record), education (usual care and a leaflet), direct mail (education and a DIY kit), or opt-in (education and the option to be sent a kit on request). Direct mailing a DIY kit was a success in boosting response rates among the screening-compliant women (screening due in the next three months) compared with education or being offered the chance to opt in (61.7% *v* 47.6% *v* 51.1%). Direct mailing also worked well among those who were overdue (35.7% *v* 15.9% *v* 18.8%).

JAMA doi:10.1001/jama.2023.21471

It's never too late to change

Modifiable risk factors are thought to account for 30-40% of dementia cases. New research suggests that it might never be too late to take action.

This two year trial of 172 adults aged 70-89 years who were at high risk of dementia (because of having at least two of factors such as poor sleep, depression, uncontrolled diabetes or high blood pressure, smoking, and social isolation) found that a personalised multi-domain risk reduction intervention (with health coaching and nurse visits) modestly improved cognitive scores, dementia risk factors, and quality of life compared with a control group who received general health education. Larger, longer trials are needed to see whether these two year gains translate into a reduced risk or delayed onset of dementia.

JAMA Intern Med doi:10.1001/jamainternmed.2023.6279

Every breath you take

Drivers and passengers inside cars can be exposed to substantial traffic-related air pollution.

This small US randomised crossover study of 16 people aged 22-45 years with normal blood pressure, took multiple blood pressure readings before, during, and up to 24 hours after a two hour city drive and measured retinal artery diameters measured as central retinal arteriolar equivalent (CRAE) before and after the drive. On two days participants drove with normal road-air in the car, while on another day they breathed air produced by HEPA filtration, which reduced the particle count by 86%. The impact of breathing unfiltered versus filtered air was evident; adjusted mean CRAE was wider in unfiltered air and blood pressure was higher (+4.5/4.7 mm Hg at 1 hour and +1.1/3.8 mm Hg at 24 hours). The study was too small to draw firm conclusions, and was limited to one place (Seattle) and one season.

Ann Intern Med doi:10.7326/M23-1309

Fresh hope

Some patients with relatively low risk myelodysplastic syndromes (MDS) need regular red blood cell transfusions to keep them going as they don't respond to, or aren't eligible for, erythropoiesis-stimulating agents (ESAs) such as epoetin. Imetelstat, a telomerase inhibitor, selectively kills malignant stem cells in the bone marrow which are the source of the problem in MDS.

In this first phase 3 trial of 178 patients with median follow-up of 19.5 months, those taking imetelstat needed fewer transfusions than those given placebo (rate difference 25%), could manage up to a year without a transfusion, and showed evidence of disease-modifying activity. The downside is that, because of the way the drug wipes out stem cells, treatment-related side effects such as neutropenia were almost universal in the imetelstat group (grade 3-4 treatment-emergent adverse effects 91% *v* 47%). On the plus side, the adverse events were reversible and manageable and there were no treatment-related deaths.

Lancet doi:10.1016/S0140-6736(23)01724-5

Saving hearts

Guidelines recommend giving thyroid hormone infusions to brain-dead (those declared dead according to neurological criteria), haemodynamically unstable people who are potential heart donors. The rationale is that brain death often causes neurohormonal deficiency, especially thyroid hormone, which starves the myocardium of energy and causes shock.

This randomised study of 838 brain-dead donors compared outcomes with thyroid versus saline infusions. There was no significant difference in the percentage who went on to donate their heart (54.9 *v* 53.2%), and graft survival at 30 days was extremely high and the same in both groups (>95%). Furthermore, the levothyroxine group had more cases of severe hypertension and tachycardia.

N Engl J Med doi:10.1056/NEJMoa2305969

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EASILY MISSED?

Developmental dysplasia of the hip in infants and children

CPD READING
0.5 HOURS

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com.

What is developmental dysplasia of the hip (DDH)?

DDH is a spectrum of conditions, ranging from a shallow acetabulum (acetabular dysplasia) with or without instability to a completely dysplastic, unstable, or dislocated hip. In most high income countries, DDH is diagnosed by physical examination, supplemented using static or dynamic ultrasound assessment, which can detect DDH across different stages.[1 2] Clinical screening alone is associated with late diagnoses, which can lead to unnecessary surgical intervention, lifelong disability, and litigation.

How common is it?

Mild forms of DDH overlap with physiological immaturity, therefore quantifying incidence remains challenging. Worldwide, estimates depend on the population studied, and in one systematic review, the incidence per 1000 live births ranged from 0.06 in Africans in Africa to 76.1 in Native Americans in Canada.[3] Population studies have shown that although 2-3% of hips have a degree of dysplasia, only 0.5 to 1 in 1000 newborns born in the UK has a unilateral, irreducible hip dislocation.[4]

Box 1 | Clinical presentation of DDH according to age

Under 2 months
- Positive Barlow or Ortolani tests

2 months or older
- Limited hip abduction when the hip is flexed to 90 degrees
- Leg length discrepancy
- Thigh skin fold asymmetry
- Positive Galeazzi sign

Mobile child
- Abnormal gait (Trendelenburg or waddling)
- Toe walking on the affected side or unequal leg lengths

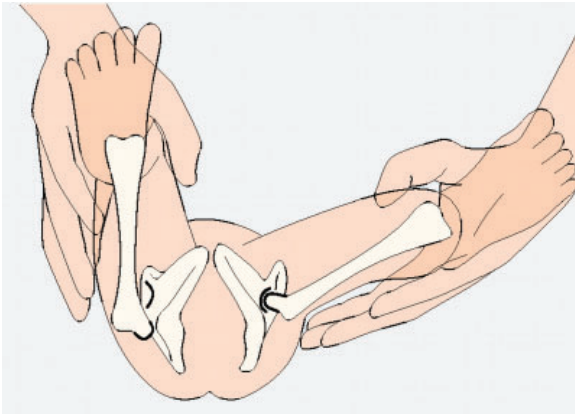

Fig 1 | Barlow test (left) and Ortolani test (right). In the Barlow test (infant's right hip) the hip is adducted and flexed to 90°, the examiner holds the distal thigh and pushes posteriorly on the hip joint. The test is positive when the femoral head is felt to slide posteriorly as it dislocates. In the Ortolani test (infant's left hip) the pelvis is stabilised by the examiner and each hip examined separately. In an infant with limited hip abduction in flexion, the hip is flexed to 90° and gently abducted while the examiner's finger lifts the greater trochanter. In a positive test the femoral head is felt to relocate into the acetabulum

How is DDH diagnosed?

In the UK, guidelines advise that newborns be clinically examined within 72 hours of birth.[1] This includes assessment of their hips, using both Ortolani and Barlow tests. If any abnormality is noted, or if risk factors are present (first degree family history of hip problems in early life, breech presentation >36 weeks of pregnancy, breech presentation at time of birth from >28 weeks), an ultrasound of the hips should be requested.[1]

Clinical examination

Clinical presentation varies according to age (box 1). The Ortolani test is performed by the examiner first stabilising the pelvis and examining each hip separately. The hip is flexed to 90° and is gently abducted with the examiner's finger lying on the greater trochanter. The test is considered positive if the femoral head relocates with a distinct clunk (fig 1). In contrast, Barlow's test is performed by adducting the hip to the midline and gently applying posterior force. A palpable clunk is felt if the hip is dislocatable (fig 1). A Barlow-positive hip indicates the femoral head is resting in the acetabulum but has pathological instability.[6]

One common cause of confusion is the significance of hip clicks during the examination. Most commonly, these are caused by stretching of ligaments around the hip or knee

WHAT YOU NEED TO KNOW

- Developmental dysplasia of the hip (DDH) is a spectrum of conditions, ranging from a shallow acetabulum with or without instability to a dysplastic, unstable, or dislocated hip
- Diagnostic accuracy of clinical examination in the newborn period and at the 6-8 week check is low
- Signs suggestive of DDH vary according to age, and use of ultrasound increases detection
- Late diagnoses increase the need for operative intervention and have long term implications for patients and their families
- Whether to screen infants selectively or universally with ultrasound remains controversial

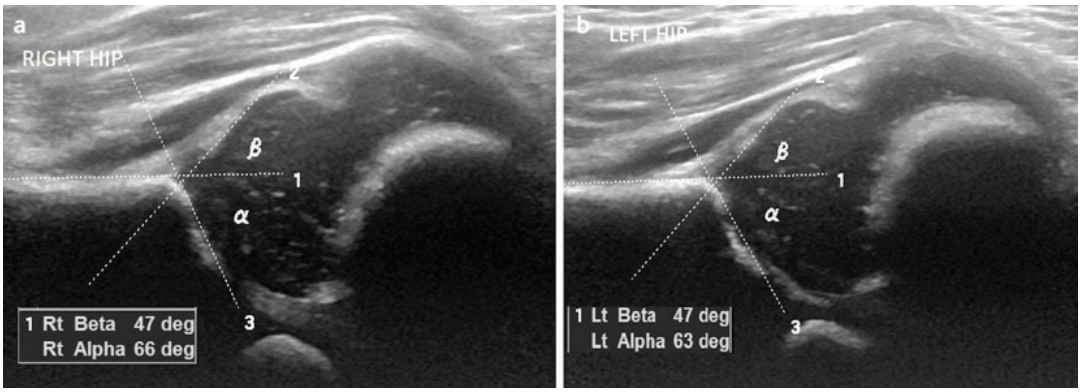

Fig 3 | Normal ultrasound of the hips with normal alpha and beta angles as per the Graf technique. The alpha angle is >60° on either side

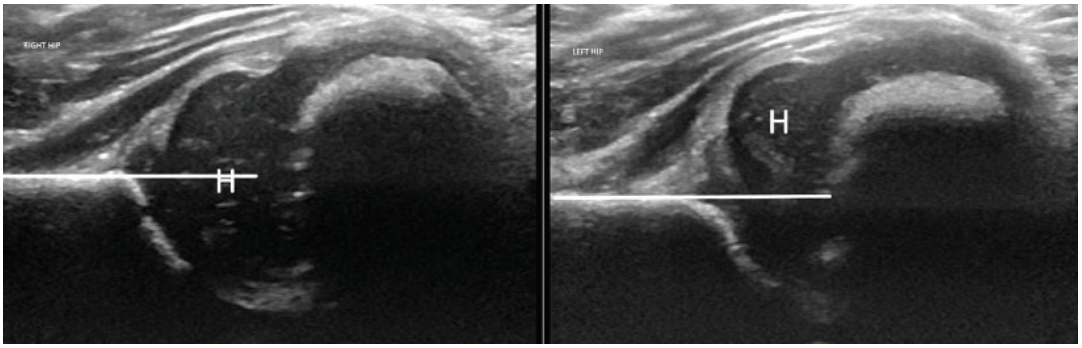

Fig 4 | Ultrasound of the hips of a 1 month old infant with a clinically dislocated left hip. Images show that about 50% of the right cartilaginous femoral head (H) lies below a line drawn along the cortex of the ilium. This line forms the base of the Graf angle. The left cartilaginous femoral head (H) lies above the ilial line.

and are benign. They are distinguishable from the clunks felt in either the Barlow or Ortolani tests.[6] If uncertain, consider re-examining an apparent hip click, and if it disappears by 2 weeks of age, no further action is required.[9]

In infants older than three months and children, the Ortolani and Barlow tests are of limited value.[10] Signs suggestive of DDH in these age groups include limited hip abduction, leg length discrepancy, and thigh skinfold asymmetry. Limitation of hip abduction, especially if unilateral, is an important physical sign of DDH from 8 weeks of age (fig 2, see bmj.com).[10] Assess leg length discrepancy with the infant in the supine position with the pelvis flat on a level surface and the hips and knees flexed to 90°. A discrepancy is indicated by unequal knee heights (Galeazzi sign).

Another common cause of confusion is the significance of asymmetrical skin folds in the buttocks or posterior thighs on ventral suspension. These may be normal in young infants, and skin fold asymmetry may be absent if there is bilateral DDH. Thus, skin fold asymmetry is unreliable in detecting DDH in infants under 3 months although it may be more useful in older infants.[11] A walking child may present with a Trendelenburg gait, where the trunk tilts towards the affected hip when weight is applied if there is unilateral DDH, or a waddling gait if there is bilateral DDH.

Radiological diagnosis

UK guidelines recommend a selective approach to ultrasound scanning, with screening in infants by 2 weeks of age if they show clinical signs of hip instability in the newborn examination.[1] Ultrasound of the hip is indicated by 6 weeks of age if the infant has relevant risk factors for DDH.[1] Ultrasound remains the recommended imaging modality for diagnosis of DDH and monitoring post-intervention in infants under 4 months as it allows visualisation of the position of the femoral head in relation to the acetabulum, without exposure to radiation.[12]

Although international consensus has not yet been reached, the Graf method is widely used to diagnose DDH on ultrasound.[2] This method uses measurement of the alpha angle, which reflects the depth of the bony acetabulum and should be greater than 60°, and the beta angle, which describes the coverage of the femoral head by the cartilaginous roof.[2] Graf I is a negative result, Graf IIa indicates hip immaturity and mandates re-scanning at 12 weeks of age, and Graf IIb and above requires prompt referral to a specialist orthopaedic service (figs 3, 4). A negative hip ultrasound under 6 weeks of age indicates that DDH is highly unlikely, with a negative predictive value of over 99%.[2 13]

In infants over 4 months of age, hip radiographs are the preferred imaging modality to diagnose DDH or monitor post-intervention.[14] The acetabular index assesses the relation between the femoral head and the acetabulum, with a normal index being 30° in unaffected newborns and a higher index indicating hip dysplasia (fig 5). After 6 months of age, femoral head ossification normally occurs, but may be delayed in infants with DDH.[14]

Why is DDH missed?

More than two thirds of newborns with DDH do not have risk factors; thus clinical examination is often relied upon to diagnose the condition.[15 16] However, examination alone has limited diagnostic accuracy. Data describing the utility of the Barlow and Ortolani tests remain hampered by few incident cases of DDH, single centre bias, and heterogeneity in screening methodology and protocols. Historical data showed that Barlow and Ortolani tests had a sensitivity of 66%, specificity of

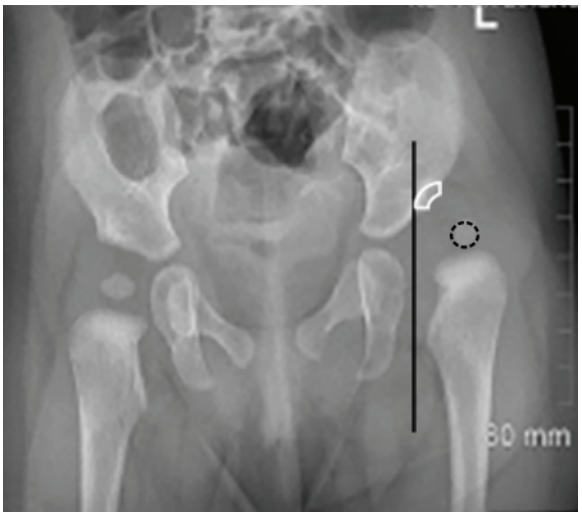

Fig 5 | Delayed presentation of DDH. X ray image of the pelvis of a 5 month old infant referred with limited left hip abduction. The right hip is normal. Severe left acetabular dysplasia is present, with superior dislocation of the left hip. The left femoral head lies lateral to the Perkin line (black vertical line) and there is pseudoarticulation with the superior left ilium (marked with the crescentic shape). The left proximal ossific nucleus (dotted circle) is smaller than the right

99.8%, and positive predictive value (PPV) of 28% in diagnosing DDH.[17-20] More recent evidence, however, suggests that the PPV for the Ortolani test may be as high as 39-61%, and for the Barlow test as low as 4%-16%, depending on the case definition used.[21] In one UK primary care cohort study of 70 071 infants with 15 years' follow-up, the overall sensitivity, specificity, PPV, and negative predictive value for the 6-8 week check was determined to be 16.7%, 99.8%, 3.5%, and 100%, respectively.[22] The diagnostic accuracies of these tests are higher when performed in the first few days of life compared with at 6-8 weeks of age, as evidenced by one UK based cohort study of 23 112 live births which found that the DDH was not identified in four out of five children at the 6-8 week check.[23]

Reliability of examination is improved when it is performed by smaller numbers of experienced staff;[24] however, even experienced healthcare professionals miss cases.[25] Midwives, health visitors, and practice nurses are increasingly performing newborn examinations and routine health screening and constitute a critical "safety net" in detecting DDH outside the newborn period.[26 27]

Box 2 | Surgical management techniques[49]

- Closed reduction—The hip is placed in 90-100° of flexion and the minimum amount of abduction is applied to maintain stable hip reduction. An adductor or psoas tenotomy is performed, followed by three to four months in a plaster cast.
- Open reduction—For children over 12 months of age or for younger children whose closed reduction has not been successful, open surgical reduction is recommended with a femoral osteotomy. Remodelling of the femoral head within the acetabulum tends to occur 12 to 18 months after the reduction of the hip.

HOW PATIENTS WERE INVOLVED IN THE WRITING OF THIS ARTICLE

We asked a parent (RC), who is the mother of a male child who was screened both clinically and by ultrasound in view of breech presentation for DDH, to read through the early drafts of the article and provide feedback. She read the paper carefully over several drafts and was surprised that current screening methods in both Ireland and the UK have significant limitations.

EDUCATION INTO PRACTICE

- How do you assess for DDH, and what do you do if your clinical examination is equivocal?
- In your local practice or hospital service, how many cases of missed DDH have there been and what steps were taken to mitigate future events?

Universal ultrasound screening or not?

Although used in some countries, the role of ultrasound as a universal screening tool remains controversial. High quality, randomised, and prospective data to accurately assess whether universal versus selective screening leads to improved clinical outcomes, and whether either is cost effective on a large-scale, are lacking. Furthermore, the development of the condition, particularly missed DDH, remains poorly understood and is a priority for future research.[28]

In the absence of high quality data, expert consensus is that universal hip ultrasound screening is cost effective, does not lead to overtreatment, and reduces long term consequences of missed DDH.[42] Similarly, a Delphi consensus study from the British Society for Children's Orthopaedic Surgery also recommended a universal ultrasound strategy.[43]

How is DDH managed?

Most mild-to-moderate DDH can resolve without treatment in early infancy, especially in physiologically immature (Graf IIa) hips.[17-31] If the hip is moderately or severely dysplastic (Graf IIb and above), refer to orthopaedic surgeons urgently for consideration of applying a splint (eg, a Pavlik harness) and ensure appropriate follow-up with the specialist teams, including physiotherapy.[6 46] The splint remains in place at all times but may be adjusted as the infant grows and the hip stabilises. Early application of a Pavlik harness is associated with success rates of greater than 90% in achieving hip reduction, and a very low risk of complications, including avascular necrosis.[47 48]

For infants who fail to stabilise after initial Pavlik harness treatment, a trial of a more rigid abduction hip (such as an Ifeld orthosis) may obviate the need for surgery.[49] Older infants with untreated DDH (often 6 to 18 months of age), or those who have failed earlier Pavlik harness treatment, may require closed reduction and hip spica casting[49] (box 2). Factors associated with better prognosis include earlier age at presentation, lower severity of dysplasia, quicker time to diagnosis and treatment, and surgical technique.[49]

Competing interests: None declared.

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A living WHO guideline on drugs for covid-19

CPD READING
0.5 HOURS

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Updates

This is the fourteenth version (thirteenth update) of the living guideline, replacing earlier versions.

Clinical question

What is the role of drugs in the treatment of patients with covid-19?

What is new?

The Guideline Development Group defined 1.5% as a new threshold for an important reduction in risk of hospitalisation in patients with non-severe covid-19. New recommendations were added for moderate risk of hospitalisation for nirmatrelvir/ritonavir, and for moderate and low risk of hospitalisation for molnupiravir and remdesivir. New pharmacokinetic evidence was included for nirmatrelvir/ritonavir and molnupiravir, supporting existing recommendations for patients at high risk of hospitalisation. The recommendation for ivermectin in patients with non-severe illness was updated in light of additional trial evidence. A new recommendation was made against the antiviral agent VV116 outside of randomised clinical trials.

The baseline risk estimates for hospital admission and mortality were updated in this 14th iteration of the guideline, where the Guideline Development Group (GDG) defined three risk categories for which the recommendations apply:

- *Patients at high risk (6%) of hospitalisation*—Includes those with diagnosed immunodeficiency syndromes, those who have undergone solid organ transplantation and are receiving immunosuppressants, and those with autoimmune illness receiving immunosuppressants.
- *Patients at moderate risk (3%) of hospitalisation*—Those over 65 years, those with obesity, diabetes and/or chronic cardiopulmonary disease, chronic kidney or liver disease, active cancer, those with disabilities, and those with comorbidities of chronic disease.
- *Patients at low risk (0.5%) of hospitalisation*—Most patients are low risk.

In this 14th iteration, the GDG defined 1.5% as a new threshold for an important reduction in risk of hospitalisation in patients with non-severe covid-19.

Nirmatrelvir/ritonavir represents a superior choice to the other drugs

Recommendations for patients with non-severe covid-19

Nirmatrelvir/ritonavir

Nirmatrelvir is a SARS-CoV protease inhibitor which prevents viral replication. It is administered orally in combination with ritonavir, a HIV protease inhibitor. Nirmatrelvir retains activity against all SARS-CoV-2 variants studied in vitro to date,[12-15] but randomised controlled trial evidence is not available for many newer variants.[13]

Update—An initial strong recommendation for patients with non-severe covid-19 at highest risk of hospitalisation, and a conditional recommendation against use of nirmatrelvir/ritonavir for patients at low risk of hospitalisation, were published in 2022. In this 14th version of the guideline, these are maintained for high and low risk groups. The GDG made a conditional recommendation in favour of treatment for the newly defined moderate risk group (3%), assuming they would find a 1.5% absolute risk reduction important. Breastfeeding and pregnant people may consider use of nirmatrelvir/ritonavir.

Recommendation 1: *For patients at high risk of hospitalisation, we recommend treatment with nirmatrelvir/ritonavir (strong recommendation).*

There is high certainty evidence of an important reduction in the absolute risk of hospitalisation and moderate certainty in a survival benefit without an increase in adverse events. Indirect comparisons in high risk patients demonstrated nirmatrelvir/ritonavir may reduce hospitalisation compared with molnupiravir (moderate certainty); little or no difference in effect was observed when compared with remdesivir (low certainty).

The GDG concluded that nirmatrelvir/ritonavir represents a superior choice to the other drugs when available and in patients in whom drug interaction is not an issue. There is no evidence for combining antiviral therapies; the GDG therefore advised against this.

Balance of benefits and harms—Beyond the benefits on reduced hospitalisations and mortality, nirmatrelvir/ritonavir may not affect time to symptom resolution (low certainty of evidence). The drug had no effect on adverse events leading to drug discontinuation (high certainty of evidence).

Values and preferences—The GDG inferred that almost all well informed patients at high risk of hospitalisation would choose to receive nirmatrelvir/ritonavir.

Applicability—Nirmatrelvir/ritonavir represents an

the bmj Visual summary

Treatments for covid-19

Overview of rapid recommendations

See an interactive version of this graphic online
https://bit.ly/BMJrrcovid

Population

This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Interventions

Disease severity

	Non-severe	Severe	Critical
	Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Risk of admission to hospital: H High 5%; M Moderate 3%; L Low 0.5%	Signs of pneumonia	Acute respiratory distress syndrome
		Signs of severe respiratory distress	Sepsis
			Septic shock

UPDATE: Several recommendations for people with non-severe disease are now stratified by how likely it is for someone to be admitted to hospital

Strong recommendations in favour

- Nirmatrelvir and ritonavir (H)
- Corticosteroids
- IL-6 receptor blockers
- Baricitinib

All three may be combined

Weak or conditional recommendations in favour

- Molnupiravir (H) — Requires mitigation strategies to reduce potential harms
- Remdesivir (H)
- Nirmatrelvir and ritonavir (M)
- Remdesivir

New recommendation

UPDATE

- VV116 — Only in research settings

Weak or conditional recommendations against

- Corticosteroids
- Molnupiravir (M) — Requires mitigation strategies to reduce potential harms
- Remdesivir (M)
- Nirmatrelvir and ritonavir (L)
- Fluvoxamine — Only in research settings
- Ruxolitinib and tofacitinib — Should be considered only if neither baricitinib nor IL-6 receptor blockers are available
- Ivermectin — Only in research settings
- Convalescent plasma — Only in research settings
- Remdesivir

Strong recommendations against

- Remdesivir (L)
- Molnupiravir (L)
- Sotrovimab
- Colchicine
- Ivermectin
- Convalescent plasma

UPDATE: Ivermectin is no longer recommended for people with non-severe disease, even in research settings

- Hydroxychloroquine
- Lopinavir-ritonavir
- Casirivimab and imdevimab

Nirmatrelvir/ritonavir represents an option for pregnant people with covid-19 to reduce the risk of disease progression

option for pregnant people with covid-19 to reduce the risk of disease progression. The GDG acknowledged the uncertainty in terms of potential serious adverse reactions in pregnant or breastfeeding people—despite no reports of such reactions in the parent or child so far in the WHO Vigibase.

Practical issues—Nirmatrelvir/ritonavir is recommended to be administered as 300 mg/100 mg orally every 12 hours for five days, as early as possible in the course of the disease. Trials excluded patients with severe kidney impairment and severe liver impairment. Clinicians should use nirmatrelvir/ritonavir with caution in such patients. Ritonavir is a perpetrator of many drug-drug interactions, warranting serious consideration.

Resource implications—Nirmatrelvir/ritonavir is unlikely to be available for all individuals who would choose to receive the treatment. Access to and appropriate use of diagnostic tests are essential for implementation.

Recommendation 2: *For patients at moderate risk of hospitalisation, we suggest treatment with nirmatrelvir/ritonavir (weak or conditional recommendation).*
There is high certainty of an important reduction in the risk of hospitalisation. A conditional recommendation was made due to the uncertainty regarding baseline risk estimates, uncertainty around GDG inferences regarding values and preferences, and likely considerable variability in values and preferences.

Recommendation 3: *For patients at low risk of hospitalisation, we suggest not to use nirmatrelvir/ritonavir (conditional or weak recommendation).*
Best estimates suggest that any benefit of nirmatrelvir/ritonavir in low risk patients with non-severe covid-19 are trivial (high certainty for mortality and hospitalisation). Nevertheless, the GDG noted the uncertainty in risk estimates, and uncertainty and variability of patient values and preferences, therefore deciding for a conditional rather than a strong recommendation.

Remdesivir

Remdesivir is a nucleoside analogue which interacts with the SARS-CoV-2 polymerase to elicit delayed chain termination during RNA genome synthesis. Remdesivir activity across variants has been stable.[14 15]

Update—A recommendation was made in 2022 suggesting treatment with remdesivir for patients at highest risk of hospitalisation. In this 14th version of the guideline, the GDG made new recommendations for patients with non-severe covid-19 at low and moderate risk of hospitalisation; the recommendation for patients at high risk is unchanged.

Recommendation 1: *For patients at high risk of hospitalisation, we suggest treatment with remdesivir (conditional or weak recommendation).*
This update was informed by additional trials confirming the benefits of remdesivir in reducing hospitalisations for patients in the high risk group, and the apparent little or no serious adverse effects. A conditional, rather than strong, recommendation was informed by the complexity of administration, and the potential of the recommendation to exercerbate costs and access inequities.

Indirect comparisons in high risk patients demonstrated remdesivir may reduce hospitalisation when compared with molnupiravir, and found little or no difference when compared with nirmaltrelvir/ritonavir (both low certainty). Remdesivir is likely to be the desirable option for specific subpopulations in patients for whom nirmatrelvir/ritonavir or molnupiravir are not options.

Balance of benefits and harms—Remdesivir probably results in an important reduction in risk of hospital admission (moderate certainty) with probably little or no impact on mortality (moderate certainty), mechanical ventilation (moderate certainty) and time to symptom resolution (low certainty). The impact on adverse events leading to discontinuation is uncertain (very low certainty). Relative to both nirmatrelvir/ritonavir and molnupiravir, there is little or no difference in mortality (high certainty). Remdesivir may reduce admission to hospital more than molnupiravir; there may be little or no difference when compared to nirmatrelvir-ritonavir (both low certainty).

Values and preferences—The GDG inferred that most well informed patients at high risk for hospitalisation would choose to receive remdesivir rather than no antiviral agent, but an appreciable minority would decline depending on their perception of the burden of administration. The GDG concluded that, because of the possible toxicity of molnupiravir and the possible superiority of remdesivir in reducing hospitalisation, the majority of patients would choose remdesivir over molnupiravir.

Applicability—Only one included trial enrolled children (aged ≥12 years); the applicability of this recommendation to children therefore remains uncertain. In the absence of trial data for children aged <12 years with weight <40 kg, the use of remdesivir in these children is not recommended. Uncertainty also remains with regard to pregnant or lactating people.

Practical issues—Remdesivir should be administered via intravenous infusion as a three day regimen; 200 mg is administered on day 1, followed by 100 mg given on days 2 and 3. Administration should be as early as possible in the course of the disease, with monitoring for allergic, infusion related, or other adverse outcomes for a brief period following infusions. Caution should be used when administering remdesivir to patients with significant liver or kidney disease.

Resource implications—The infusion schedule represents a feasibility challenge in outpatient settings, and availability of such treatment facilities may be limited. This reinforces that remdesivir should be reserved for those at high risk, and is an important consideration in choices between remdesivir and both nirmatrelvir/ritonavir and molnupiravir.

Recommendation 2: *For patients at moderate risk of hospitalisation, we suggest not to use remdesivir (conditional or weak recommendation).*
The conditional recommendation against represents the GDG's view that remdesivir will represent a good

choice only in those in whom nirmatrelvir/ritonavir is unavailable or involves problematic interactions, and even then only in a minority of such individuals.

Recommendation 3: *For patients at low risk of hospitalisation, we recommend not to use remdesivir (strong recommendation).*

Molnupiravir

Molnupiravir is an orally administered antiviral which inhibits replication of SARS-CoV-2 with an in vitro potency broadly similar to remdesivir.[17 18] This inhibitory effect has been shown in animal studies, with possibly greater efficacy when combined with favipiravir.[19-21] New variants of SARS-CoV-2 have shown major differences in sequences for the viral spike protein but not the RNA polymerase targeted by molnupiravir; the drug's activity across variants has therefore been stable. In vitro and animal studies have suggested the possibility of carcinogenesis; no human data with long term follow-up are available regarding this.

Update—In this 14th version of the guideline, the GDG maintained a conditional recommendation in favour of use for patients with non-severe illness at high risk of hospitalisation, given an updated baseline risk of admission. Conditional recommendations were made against its use in patients with non-severe covid-19 at moderate and low risks of hospitalisation.

Recommendation 1: *For patients at high risk of hospitalisation, we suggest treatment with molnupiravir (conditional or weak recommendation).*

The GDG emphasised moderate certainty evidence of an important reduction in the absolute risk of hospitalisation, and a marginal but important reduction in the risk of death without an increased risk of adverse effects (high certainty). A combination of safety concerns based on preclinical data, values and preferences, and feasibility contributed to the conditional recommendation.

The GDG considered that nirmatrelvir/ritonavir and remdesivir represent superior choices to molnupiravir due to greater reductions in hospitalisation and due to safety concerns with molnupiravir.

Balance of benefits and harms—Molnupiravir probably reduces admission to hospital, mortality, and time to symptom resolution (all moderate certainty). The drug may have no important effect on mechanical ventilation (low certainty) and has no important effect on adverse effects leading to drug discontinuation (high certainty). However, potential long term harms remain uncertain. These include a risk of malignancy based on preclinical data (very low certainty) and emergence of resistance based on its mechanism of action.

Values and preferences—The GDG inferred that most well informed patients at high risk of hospitalisation would choose molnupiravir over no antiviral treatment.

Applicability—Due to evidence of impact on growth plate thickness and decreased bone formation in some animal studies, molnupiravir should not be used in children. Since molnupiravir elicited embryo-fetal lethality and teratogenicity in offspring when given to pregnant animals, it should not be used in pregnant or breastfeeding people. Uncertainty remains regarding consequences to children conceived by fathers receiving or having recently received molnupiravir. The unknown long term risk of genotoxicity is likely to be higher in younger patients compared with older patients; thus its use in younger adults not at high risk should be avoided.

Practical issues—In the trials, molnupiravir was dosed as 800 mg orally every 12 hours for five days, and administered within five days of symptom onset; it should be used as early as possible from symptom onset.

Resource implications—Molnupiravir is unlikely to be available for all individuals who, given the option, would choose to receive it. This reinforces that molnupiravir should be reserved for those at high risk.

Recommendation 2: *For patients with non-severe covid-19 at moderate risk of hospitalisation, we suggest against treatment with molnupiravir (conditional or weak recommendation).*

Recommendation 3: *For patients with non-severe covid-19 at low risk of hospitalisation, we recommend against treatment with molnupiravir (strong recommendation).*

Recommendations against therapeutics applicable across disease severities

VV116

VV116 is a nucleoside prodrug which, similar to remdesivir, induces chain termination (though the drug is different from remdesivir in chemical activity, in vitro antiviral activity, pharmacokinetic profiles, and dosing regimens).

Status—A new recommendation was made in the current iteration against the use of VV116 except in the context of a clinical trial, given the high degree of uncertainty regarding its effects on patient important outcomes of most critical importance.

Ivermectin

Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate gated chloride channels. We currently lack persuasive evidence of a mechanism of action for ivermectin in covid-19; any observed clinical benefit would be unexplained.

Update—In this 14th iteration, the GDG considered new trial evidence that resulted in updated recommendations for patients with non-severe illness.

Recommendation 1: *For patients with non-severe covid-19, we recommend not to use ivermectin (strong recommendation).*

Recommendation 2: *For patients with severe or critical covid-19, we recommend not to use ivermectin except in the context of a clinical trial (recommended only in research settings).*

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The GDG included patients who previously had covid-19. Their perspectives were crucial in considering the values and preferences associated with the various treatments.

Competing interests: See bmj.com.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.m3379

CASE REVIEW

A pigmented macule on the palm

A 4 year old boy was brought to the paediatric dermatology department by his parents because they had noticed a small light brown spot on his left palm, which had been growing progressively over the past year. The child had been seen previously by a dermatologist, who suspected melanoma and referred him. The lesion had shown no signs of prior inflammation or trauma. Apart from palm hyperhidrosis (excessive sweating), the child was in good health. He had no family history of similar conditions, and had not travelled abroad.

On examination, a well defined brown macule was visible on the index finger side of the left palm, measuring 2.0 × 1.2 cm (fig 1). No other skin or mucous membrane lesions were detected. Dermoscopy revealed a reticular pigmentation consisting of thin bundles of brown spicules arranged in parallel lines in certain peripheral areas (fig 2). Given the acral location of the macule and its progressive growth, a histopathological examination was conducted to rule out melanoma. The results of the histopathology examination indicated the presence of hyphae in the stratum corneum.

1 What are the differential diagnoses?

2 What is the most likely diagnosis?

3 How would you manage this condition?

Submitted by Huan He and Dan Deng

Parental consent obtained.

Cite this as: *BMJ* 2023;383:e077135

Fig 1 | Well circumscribed brown macule measuring 2.0 × 1.2 cm on the index finger side of the left palm

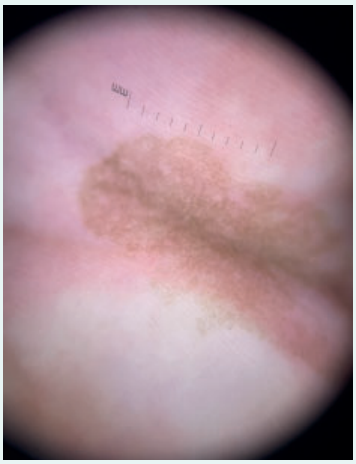

Fig 2 | Dermoscopic view showing reticular-like pigmentation comprised of thin bundles of brown spicules, arranged in parallel lines in some peripheral areas

answers

CASE REVIEW **A pigmented macule on the palm**

1 What are the differential diagnoses?

Differential diagnoses include tinea nigra, pigmented lesions such as junctional melanocytic nevi and acral lentiginous malignant in situ melanoma, and inflammatory conditions such as fixed drug eruption, post-inflammatory hyperpigmentation, or discoloration caused by chemical products, pigments, and dyes. Dermoscopy helps differentiate between these conditions. Typical dermoscopic features of tinea nigra include a reticular-like line pattern that does not correspond to the normal skin anatomy. While the parallel ridge pattern may suggest acral melanoma, the absence of colour gradation is a crucial distinguishing characteristic that helps differentiate tinea nigra from malignant melanoma. Pathological examination can aid in the differential diagnosis

2 What is the most likely diagnosis?

Tinea nigra palmaris.

Tinea nigra is a rare superficial fungal infection characterised by light brown to black macules, and primarily affects the palms of the hands and occasionally the soles of the feet. Macules are typically oval or irregularly shaped with well defined borders, and often lack scaling. The macules may exhibit a mottled colour with the darkest pigmentation at the advancing edges. The appearance of the macules can vary throughout the day, with increased pigmentation in the morning and gradual fading throughout the day. This change in pigmentation is associated with the natural clearance of the fungus from the affected area during daily activities. The main causative species is *Hortaea werneckii*, but *Stenella araguata* and *Curvularia lunata* are less common causes. Tinea nigra is more common in children.

Diagnosis is confirmed through microscopic examination of skin scrapings, revealing pigmented hyphae. Growth of dematiaceous mould on culture media can also confirm the diagnosis

3 How would you manage this condition?

Management typically involves application of topical antifungals (eg, miconazole, ketoconazole, bifonazole, and terbinafine) for at least two to four weeks to prevent recurrence.

LEARNING POINTS

- Tinea nigra is an uncommon superficial fungal infection characterised by pigmentary lesions that may resemble melanoma.
- Dermoscopy is a valuable non-invasive diagnostic tool for identifying tinea nigra.
- Management involves treatment with topical antifungals.

PATIENT OUTCOME

See bmj.com.

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LEARNING MODULE

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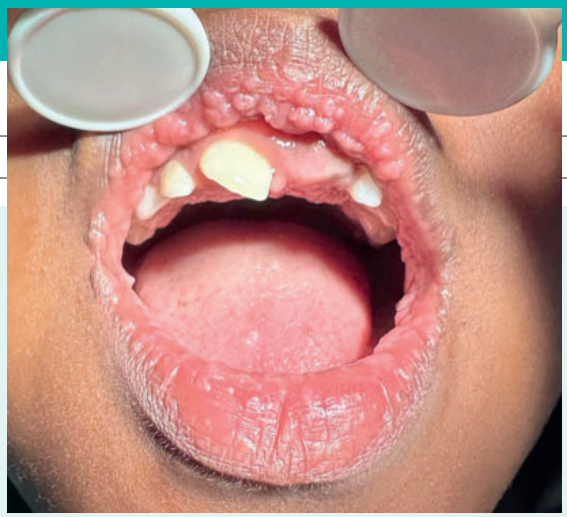
MINERVA

A Heck to check



This image shows widespread asymptomatic, soft, raised papules over the oral mucosa and lips of a 9 year old girl. The papules had been present from early childhood and became more prominent when she consumed citrus and spicy stimulants. Her mother reported a history of similar lesions during her childhood, which had regressed over time.

Focal epithelial hyperplasia, also known as Heck's disease, is a rare oral condition caused by human papillomavirus. It more commonly affects female adolescents, with studies suggesting that environmental influences and a genetic predisposition play a role. The diagnosis was confirmed by an incisional biopsy sample, which showed squamous mucosa lined by hyperplastic squamous epithelium displaying regional parakeratosis, acanthosis, and vacuolisation of epithelial cells. The cells were positive for human papillomavirus using in situ hybridisation. Heck's disease is self-limiting and patients can be counselled on the benign nature of the lesions. Excision for aesthetic or functional purposes can be considered if several lesions are present.

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If you would like to write a Minerva picture case, please see our author guidelines at bit.ly/29HCBAL and submit online at bit.ly/29yyGSx

Genetics of postpartum depression

Despite data from 20 000 cases of postpartum depression and three times that number of controls, a meta-analysis of genetic association studies fails to identify a single nucleotide polymorphism of genome-wide significance. This is something of a puzzle because twin studies have suggested that the condition has a heritability of more than 50%. The investigators say that larger studies are needed (*Am J Psychiatry* doi:10.1176/appi.ajp.20230053).

Mediterranean lifestyle

In the 1960s, Ancel Keys's cross cultural comparisons showed that people living in Mediterranean countries experienced a low mortality from cardiovascular disease, and gave rise to the idea that a diet low in saturated fat and rich in vegetables is especially healthy. This seems to be true even in countries a long way from the Mediterranean. Among 110 000 middle aged and older participants in the UK Biobank cohort, those who stuck most closely to a Mediterranean lifestyle had the lowest all cause and cancer mortality (*Mayo Clin Proc* doi:10.1016/j.mayocp.2023.05.031).

Attention deficit/hyperactivity disorder

Childhood behaviour problems suggestive of attention deficit/hyperactivity disorder are associated with multiple cardiovascular risk factors in midlife, including greater body mass index, higher blood pressure, raised triglycerides, and cigarette smoking. This is from a recent report from the National Childhood Developmental Study, a long running investigation of people born in the UK in 1958, who have been assessed at intervals ever since (*Br J Psychiatry* doi:10.1192/bjp.2023.90).

Peripheral arterial disease in people with type 2 diabetes

No surprises from a longitudinal investigation of 150 000 people on the Swedish diabetes register. Those whose risk factors (blood pressure, low density lipoprotein cholesterol, glycated haemoglobin, estimated glomerular filtration rate, and smoking) were at recommended levels were only slightly more likely to develop incident peripheral arterial disease than matched controls without diabetes. In contrast, people with five risk factors above target were 10 times more likely to develop arterial disease (*Diabetes Care* doi:10.2337/dc23-1198).

Hazardous selfies

Minerva sometimes finds it hard to avoid *Schadenfreude* when she hears about a mishap involving a smartphone, a photogenic location, and an influencer keen to impress social media followers. But selfie related accidents can have tragic outcomes, and effective methods of prevention are urgently needed. Fatalities most commonly result from falls from height and drowning. Warning signs and "no selfie" zones may help, but why not use GPS data on smartphones to trigger an alert in selfie hotspots? (*J Med Internet Res* doi:10.2196/47202)

Smartphone alerts in selfie hotspots could help prevent tragic accidents

Early exposure to antibiotics

Children who were exposed to antibiotics, either in fetal life or in the first three months of postnatal life, are slightly more likely to develop atopic dermatitis, according to an analysis of UK primary care databases. The strongest association for an individual antibiotic was with penicillin for both fetal and childhood exposure. The link was stronger in children without a family history of atopic dermatitis (*Br J Dermatol* doi:10.1093/bjd/ljad428).

Guillain-Barré syndrome after covid-19 infection and vaccination

Many infections are associated with Guillain-Barré syndrome, and SARS-CoV-2 is no exception. A large case-control study from Israel reports an odds ratio of 6 for Guillain-Barré syndrome following covid-19 infection (*Neurology* doi:10.1212/WNL.0000000000207900). On the other hand, receiving the Pfizer-BioNTech covid-19 vaccine was protective. Nationwide data from France, analysed in a self-controlled case series design, confirm the safety of mRNA vaccines as far as Guillain-Barré is concerned. However, the first generation adenoviral vector vaccines against covid-19 did carry a small increased risk of Guillain-Barré syndrome, estimated at around six cases per million persons receiving a first dose of vaccine (*Neurology* doi:10.1212/WNL.0000000000207847).

Cite this as: *BMJ* 2023;383:p2825