JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

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RESULTS

A total of 13,347 patients were enrolled, with a median crystalloid volume administered in the emergency department of 1079 ml and 88.3% of the patients exclusively receiving the assigned crystalloid. The number of hospital-free days did not differ between the balanced-crystalloids and saline groups (median, 25 days in each group; adjusted odds ratio with balanced crystalloids, 0.98; 95% confidence interval [CI], 0.92 to 1.04; P=0.41). Balanced crystalloids resulted in a lower incidence of major adverse kidney events within 30 days than saline (4.7% vs. 5.6%; adjusted odds ratio, 0.82; 95% CI, 0.70 to 0.95; P=0.01).

CONCLUSIONS

Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SALT-ED ClinicalTrials.gov number, NCT02614040.)

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REVIEW

Mycobacterium tuberculosis: Pathogenesis and therapeutic targets

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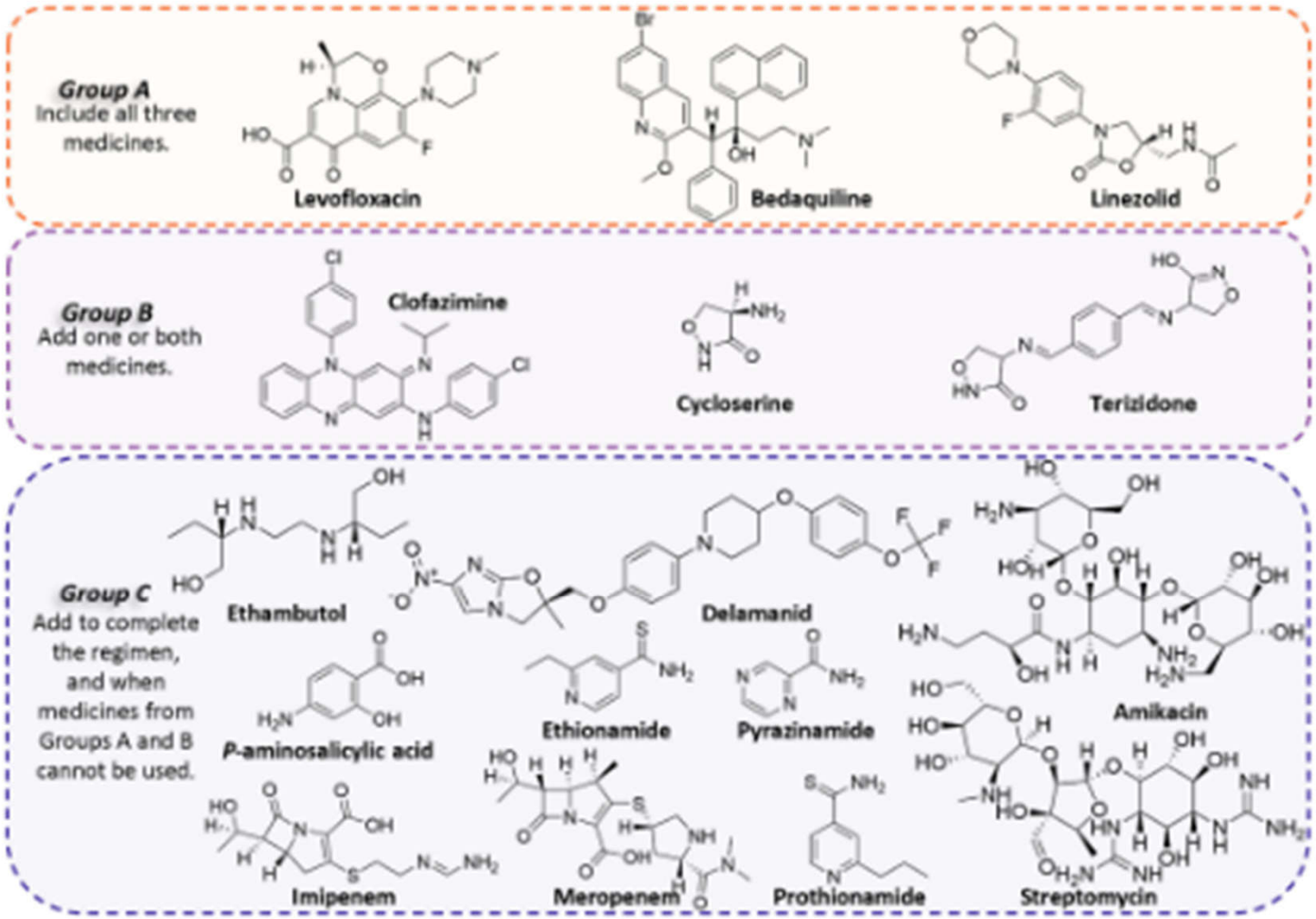
Abstract

Tuberculosis (TB) remains a significant public health concern in the 21st century, especially due to drug resistance, coinfection with diseases like immunodeficiency syndrome (AIDS) and coronavirus disease 2019, and the lengthy and costly treatment protocols. In this review, we summarize the pathogenesis of TB infection, therapeutic targets, and corresponding modulators, including first-line medications, current clinical trial drugs and molecules in preclinical assessment. Understanding the mechanisms of *Mycobacterium tuberculosis* (*Mtb*) infection and important biological targets can lead to innovative treatments. While most antitubercular agents target pathogen-related processes, host-directed therapy (HDT) modalities addressing immune defense, survival mechanisms, and immunopathology also hold promise. *Mtb*'s adaptation to the human host involves manipulating host cellular mechanisms, and HDT aims to disrupt this manipulation to enhance treatment effectiveness. Our review provides valuable insights for future anti-TB drug development efforts.


Group A
Include all three medicines.
Levofloxacin
Bedaquiline
Linezolid
Group B
Add one or both medicines.
Clofazimine
Cycloserine
Terizidone
Group C
Add to complete the regimen, and when medicines from Groups A and B cannot be used.
Ethambutol
Delamanid
P-aminosalicylic acid
Ethionamide
Pyrazinamide
Amikacin
Imipenem
Meropenem
Prothionamide
Streptomycin

option to Group A and B drugs.

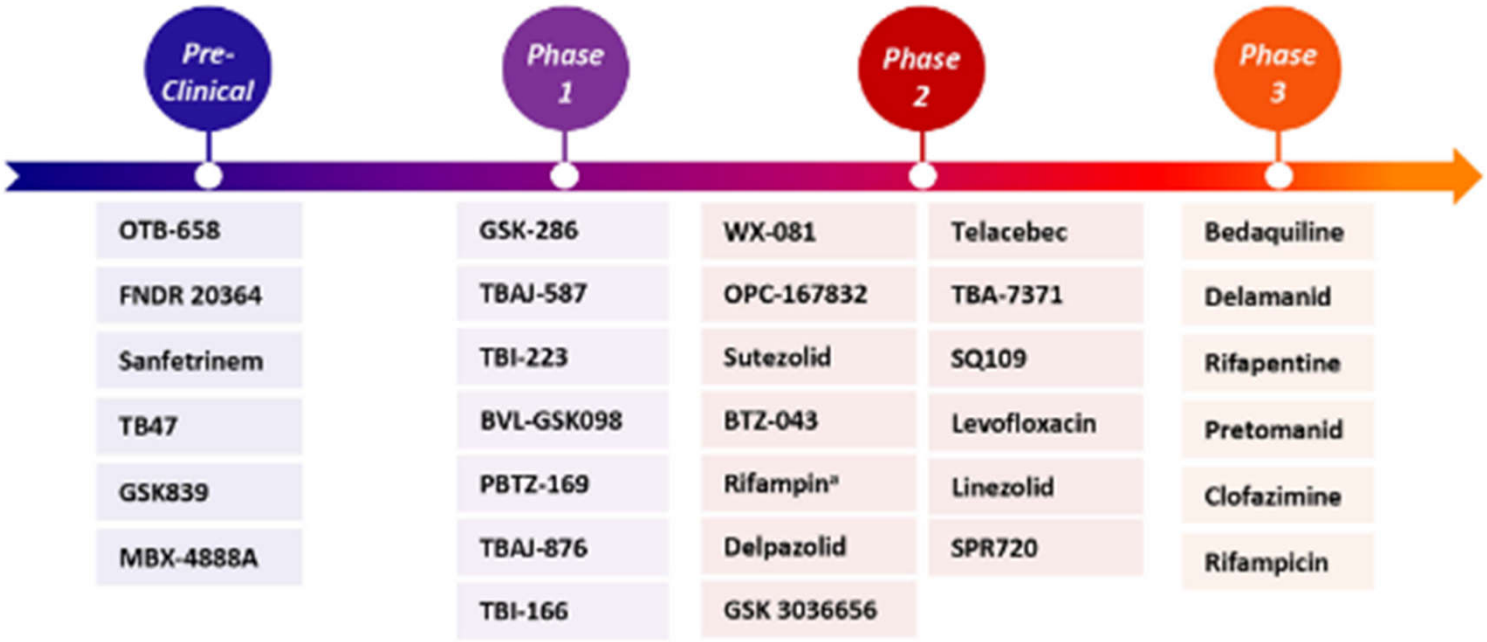


FIGURE 2 Current global clinical pipeline of new tuberculosis drugs based on information provided by the Working Group for New TB Drugs (WGND).[156] [a]Trial of high-dose Rifampin in patients with TB.

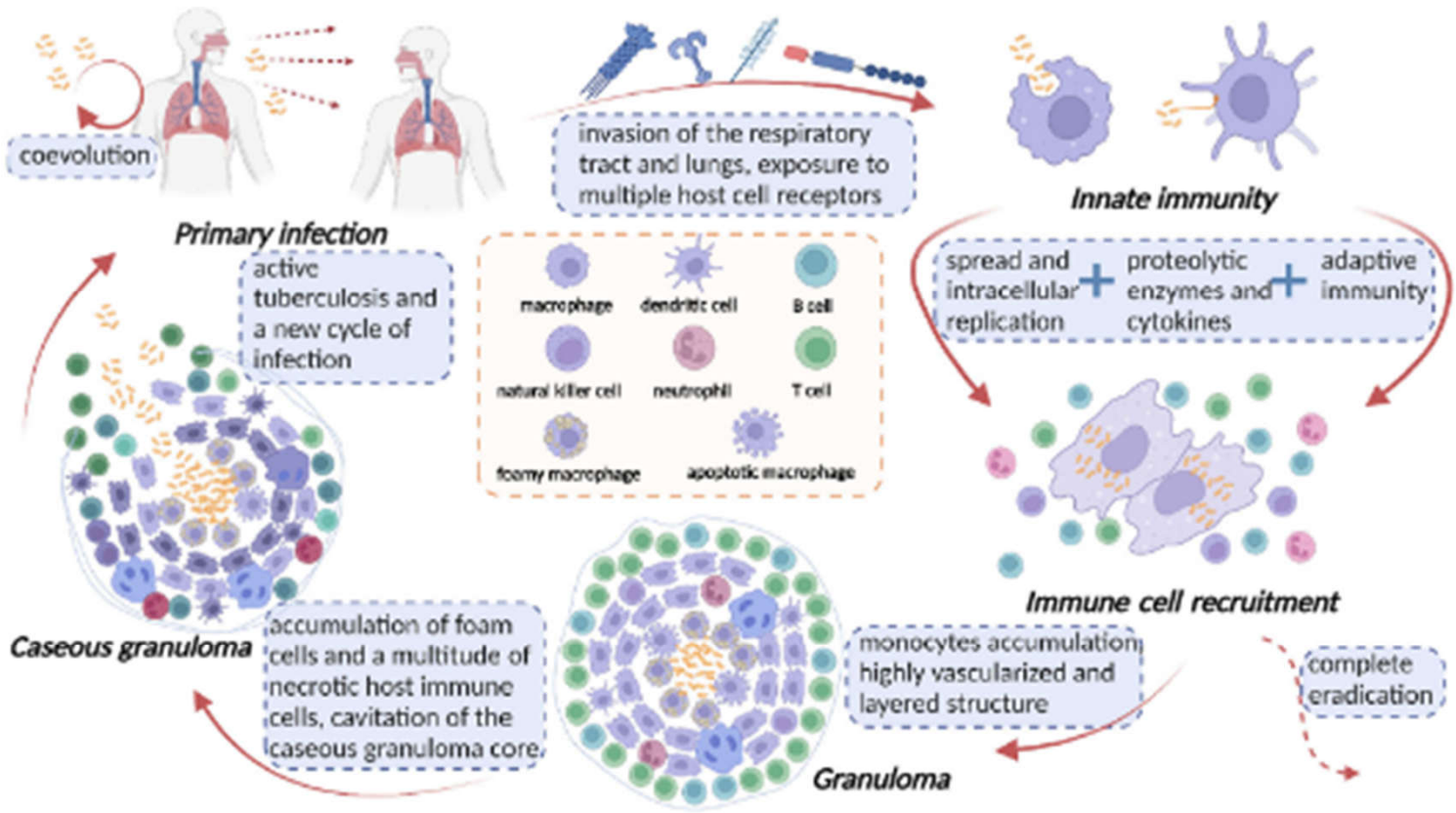


FIGURE 3 Pathophysiology of pulmonary TB. Upon entering the respiratory tract and lungs of the host, *Mtb* incites an innate immune response and is engulfed by pivotal immune cells such as macrophages and dendritic cells. Subsequently, *Mtb* replicates within these cells as more immune cells are recruited to the site of infection. Whilst it is possible for the host to completely eliminate *Mtb* at this stage, the formation of solid granulomas is often promoted. These granulomas are composed of foam cells derived from macrophages, as well as a

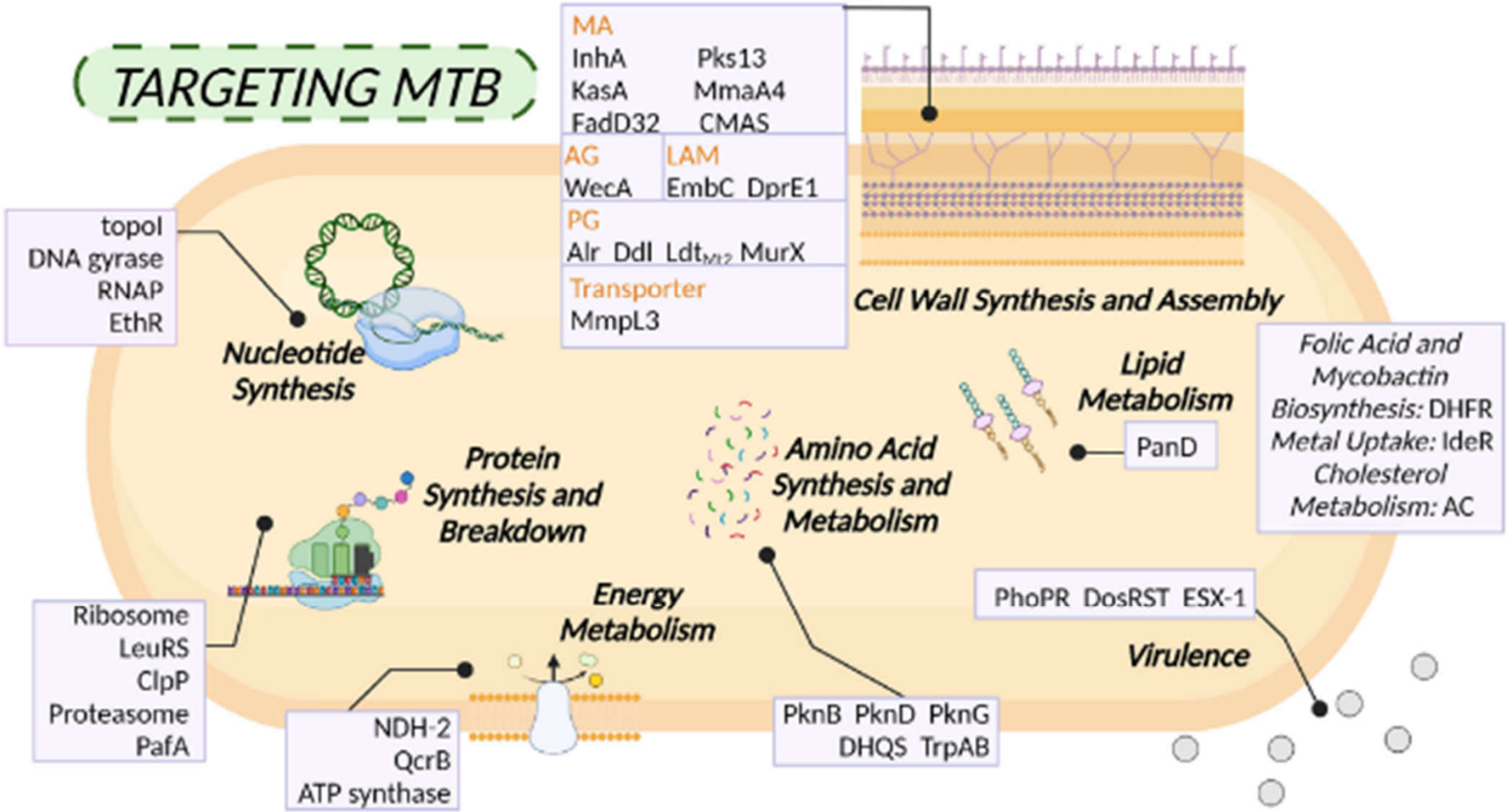


FIGURE 4 Overview of antituberculosis targets aimed at *Mtb*. Disruption of crucial pathways in *Mtb*, such as cell wall synthesis and assembly, protein synthesis and breakdown, and energy metabolism, has been regarded as a potent strategy for combating tuberculosis.

gical targets and inhibitors targeting *Mtb*.

tion	Target	Typical compound	Drug stage for TB
MA[a] biosynthesis	Enoyl-acyl carrier protein reductase (InhA)	Isoniazid[38]	Approved
		Ethionamide[39]	Approved
	β-Ketoacyl synthase (KasA)	Thiolactomycin[66–69]	Biological test
	Fatty acid degradation protein D32 (FadD32)	Quinoline-2-carboxamide[78]	Biological test
	Polyketide synthase 13 (Pks13)	TAM16[79]	Biological test
	Mycolic acid methyltransferase 4 (MmaA4)	SADAH[88]	Biological test
	Cyclopropane mycolic acid synthase (CMAS)	/	In silico docking
AG biosynthesis	*N*-acetylglucosamine-1-phosphate transferase (WecA)	CPZEN-45[97]	Preclinical
LAM biosynthesis	Arabinosyl transferase C (EmbC)	Amikacin[106]	Approved
	Decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1)	PBTZ-169[110]	Phase I
		OPC-167832[111]	Phase II
		TBA-7371[112]	Phase II
		BTZ-043[113]	Phase II
PG biosynthesis	Alanine racemase (Alr)	Cycloserine[130,131]	Approved
	D-alanyl-D-alanine ligase (Ddl)		
	L,D-transpeptidase type 2	Meropenem[136]	Approved

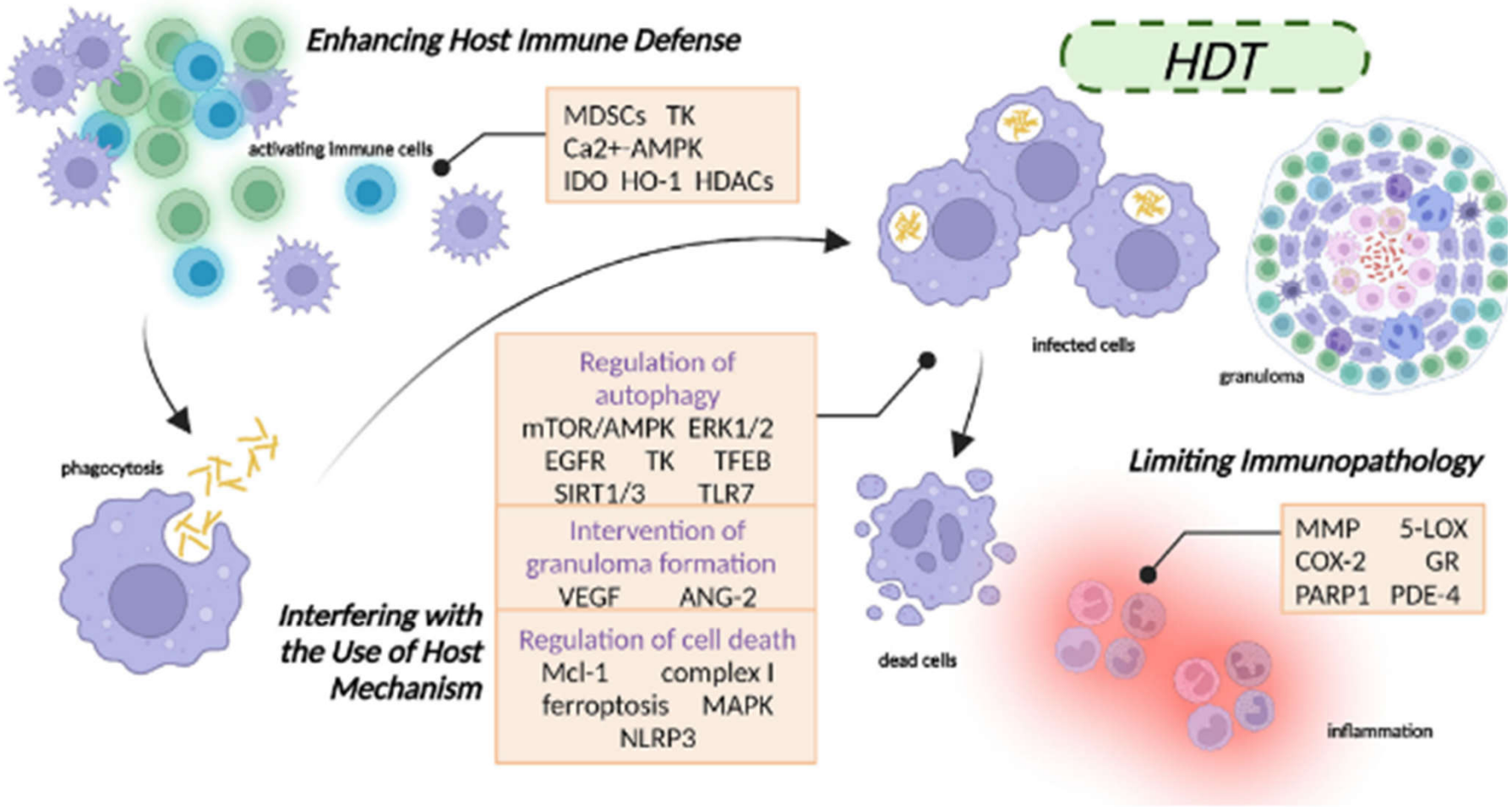


FIGURE 5 Overview of the host-directed therapies (HDT) addressed. At the level of the host, targeting important processes such as immune defense, the use of host mechanism by *Mtb*, and inflammation regulation are invigorated to address and overcome drug resistance. The elements in the figure were drawn using BioRender online tool (https://biorender.com).

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ORIGINAL ARTICLE

Observational Study

Lowering the threshold of alanine aminotransferase for enhanced identification of significant hepatic injury in chronic hepatitis B patients

Open Access Review

Transaminase Elevations during Treatm
Infection: Safety Considerations and Ro

by Andrew Vaillant

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hat 50.22% of patients were classified as GZ, and 63.7% of GZ patients developed SHI. The t lowering the ALT treatment thresholds to the American Association for the Study of Liver ent criteria (35 U/L for men and 25 U/L for women) can more accurately identify patients r damage in the GZ phases. In total, the proportion of patients with ALT ≤ 40 U/L who rapy was 64.86% [(221 + 294)/794]. When we lowered the ALT treatment threshold to the new nen and 19 U/L for women), the same outcome was revealed, and the proportion of patients who required antiviral therapy was 75.44% [(401 + 198)/794]. Additionally, the proportion of ients under 30 years old and increased to 55.3% in patients over 30 years old ($P = 0.136$).

est the importance of redefining the natural phases of CHB and using new ALT treatment diagnosis and management of CHB patients in the GZ phases.

patitis B; Grey zone; Indeterminate phase; Alanine aminotransferase; Antiviral therapy

ractice, 27.8%-55% of chronic hepatitis B patients fall into the "grey zone" or "indeterminate phase" diagnostic criteria of the traditional stages. Additionally, there is still debate regarding how best to GZ) patients and the advantages of antiviral therapy. Hence, we evaluated the clinical and histological dditionally explored the impact of adjusting the threshold of alanine aminotransferase (ALT) in liver injury among GZ patients. Based on these data, lowering ALT thresholds can more accurately ignificant hepatic injury at an earlier stage and reduce the need for unnecessary liver biopsies

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

- Three new modifiable risk factors for dementia
  - New evidence supports adding three modifiable risk factors—excessive alcohol consumption, head injury, and air pollution—to our 2017 *Lancet* Commission on dementia prevention, intervention, and care life-course model of nine factors (less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and infrequent social contact).
- Modifying 12 risk factors might prevent or delay up to 40% of dementias.
- Be ambitious about prevention
  - Prevention is about policy and individuals. Contributions to the risk and mitigation of dementia begin early and continue throughout life, so it is never too early or too late. These actions require both public health programmes and individually tailored interventions. In addition to population strategies, policy should address high-risk groups to increase social, cognitive, and physical activity; and vascular health.
- Specific actions for risk factors across the life course
  - Aim to maintain systolic BP of 130 mm Hg or less in midlife from around age 40 years (antihypertensive treatment for hypertension is the only known effective preventive medication for dementia).
  - Encourage use of hearing aids for hearing loss and reduce hearing loss by protection of ears from excessive noise exposure.
  - Reduce obesity and the linked condition of diabetes. Sustain midlife, and possibly later life physical activity.
  - Addressing other putative risk factors for dementia, like sleep, through lifestyle interventions, will improve general health.
- Tackle inequality and protect people with dementia
  - Many risk factors cluster around inequalities, which occur particularly in Black, Asian, and minority ethnic groups and in vulnerable populations. Tackling these factors will involve not only health promotion but also societal action to improve the circumstances in which people live their lives. Examples include creating environments that have physical activity as a norm, reducing the population profile of blood pressure rising with age through better patterns of nutrition, and reducing potential excessive noise exposure.
  - Dementia is rising more in low-income and middle-income countries (LMIC) than in high-income countries, because of population ageing and higher frequency of potentially modifiable risk factors. Preventative interventions might yield the largest dementia reductions in LMIC.

For those with dementia, recommendations are:

- Provide holistic post-diagnostic care
  - Post-diagnostic care for people with dementia should address physical and mental health, social care, and support. Most people with dementia have other illnesses and might struggle to look after their health and this might result in potentially preventable hospitalisations

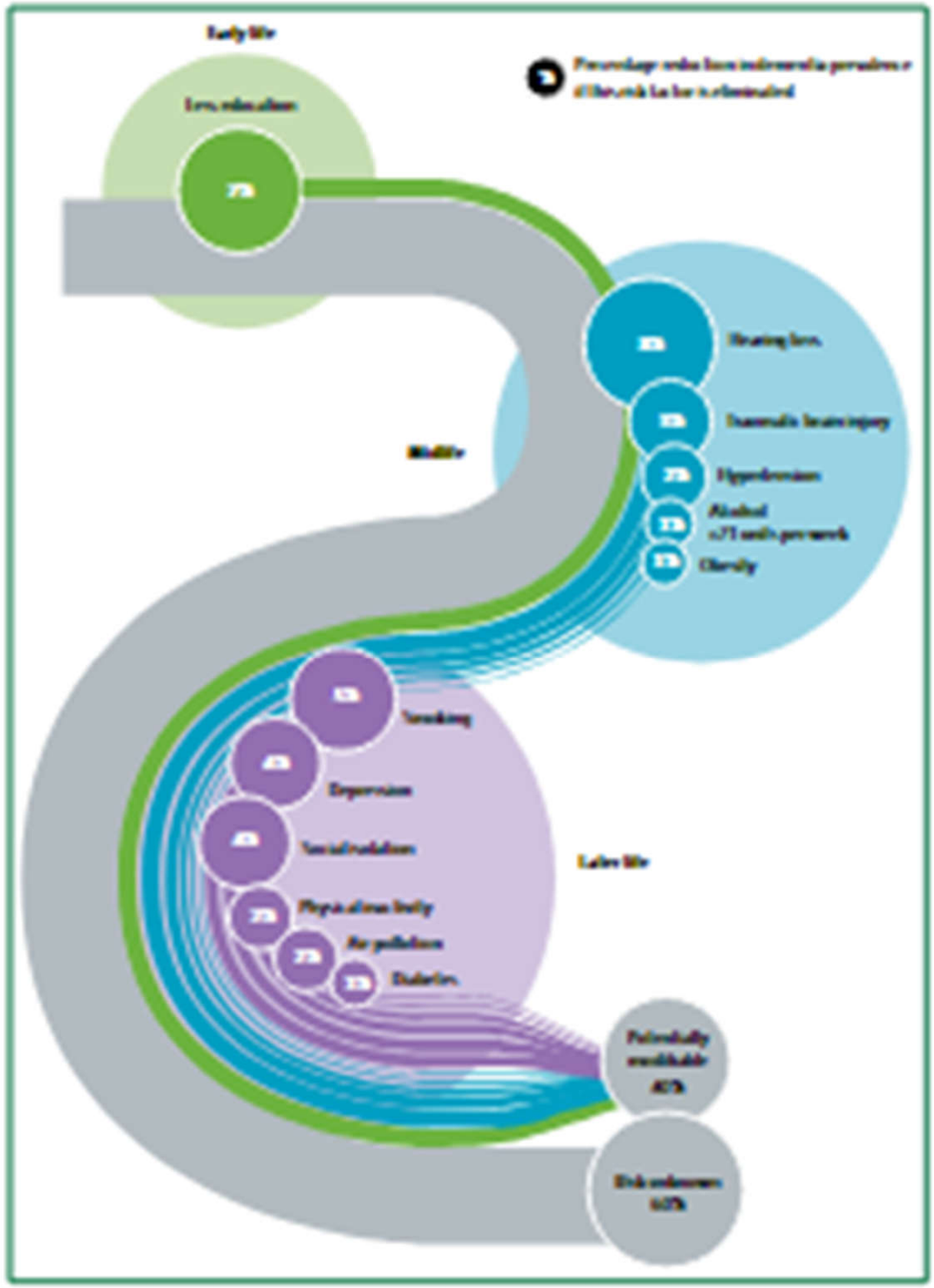


Figure 2. Population attributable fraction of potentially modifiable risk factors for dementia

Panel: Recommended strategies for dementia risk reduction

Risks are particularly high in more socially disadvantaged populations including in Black, Asian, and minority ethnic groups.

Population-wide

- Prioritise childhood education for all, worldwide
- Implement social public health policies that reduce hypertension risk in the entire population
- Develop policies that encourage social, cognitive, and physical activity across the life course for all (with no evidence for any specific activities being more protective)
- Scrutinise the risks for hearing loss throughout the life course, to reduce the risk of exposure to this risk factor
- Reduce the risk of serious brain trauma in relevant settings, including occupational and transport
- National and international policies to reduce population exposure to air pollution
- Continue to strengthen national and international efforts to reduce exposure to smoking, both for children and adults, and to reduce uptake and encourage cessation

Targeted on individuals

- Treat hypertension and aim for systolic blood pressure <130 mm Hg in midlife
- Use hearing aids for hearing loss; we need to help people wear hearing aids as many find them unacceptable, too difficult to use, or ineffective
- Avoid or discourage drinking 21 or more units of alcohol per week
- Prevent head trauma where an individual is at high risk
- Stopping smoking is beneficial regardless of age
- Reduce obesity and the linked condition of diabetes by healthy food availability and

Original Research
Cardiac Imaging

Prognostic Value of Coronary CT Angiography–derived Fractional Flow Reserve on 3-year Outcomes in Patients with Stable Angina

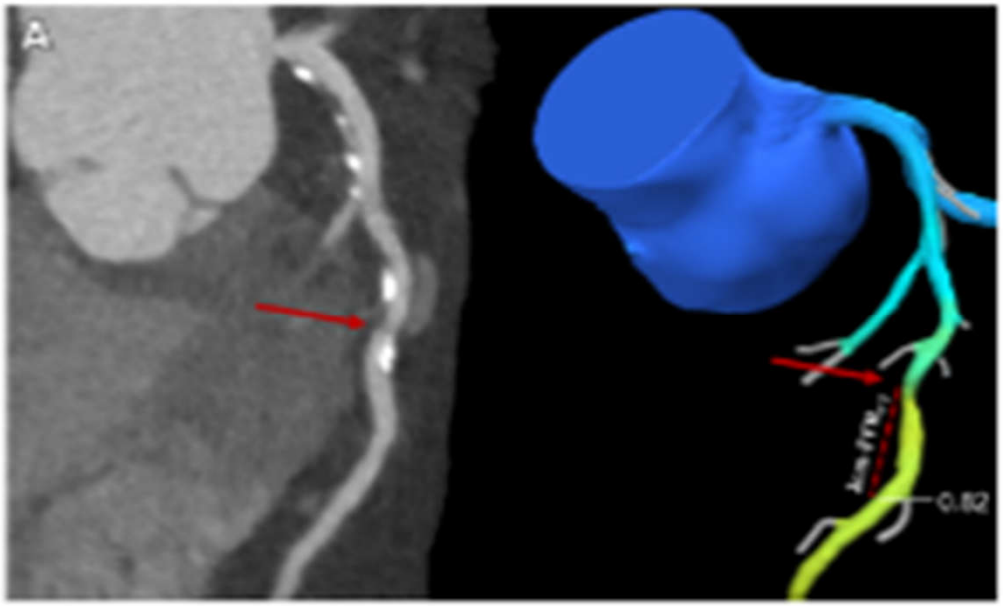
an abnormal test result. The primary end point was a composite of all-cause death and nonfatal spontaneous myocardial infarction. E
rates were estimated using the one-sample binomial model, and relative risk was compared between participants stratified by results o
coronary CTA–derived FFR.

Results: This study included 900 participants: 523 participants with normal results (mean age, 64 years ± 9.6 [SD]; 318 male par
pants) and 377 with abnormal results from coronary CTA–derived FFR (mean age, 65 years ± 9.6; 264 male participants). The pr
ry end point occurred in 11 of 523 (2.1%) and 25 of 377 (6.6%) participants with normal and abnormal coronary CTA–derived
results, respectively (relative risk, 3.1; 95% CI: 1.6, 6.3; $P < .001$). In participants with high CAC, the primary end point occurred
in four of 182 (2.2%) and 19 of 212 (9.0%) participants with normal and abnormal coronary CTA–derived FFR results, respecti
(relative risk, 4.1; 95% CI: 1.4, 11.8; $P = .001$).

Conclusion: In individuals with stable angina, a normal coronary CTA–derived FFR test result identified participants with a
low 3-year risk of all-cause death or nonfatal spontaneous myocardial infarction, both in the overall cohort and in participants wit
high CAC scores.

Clinical trial registration no. NCT02499679

Supplemental material is available for this article.



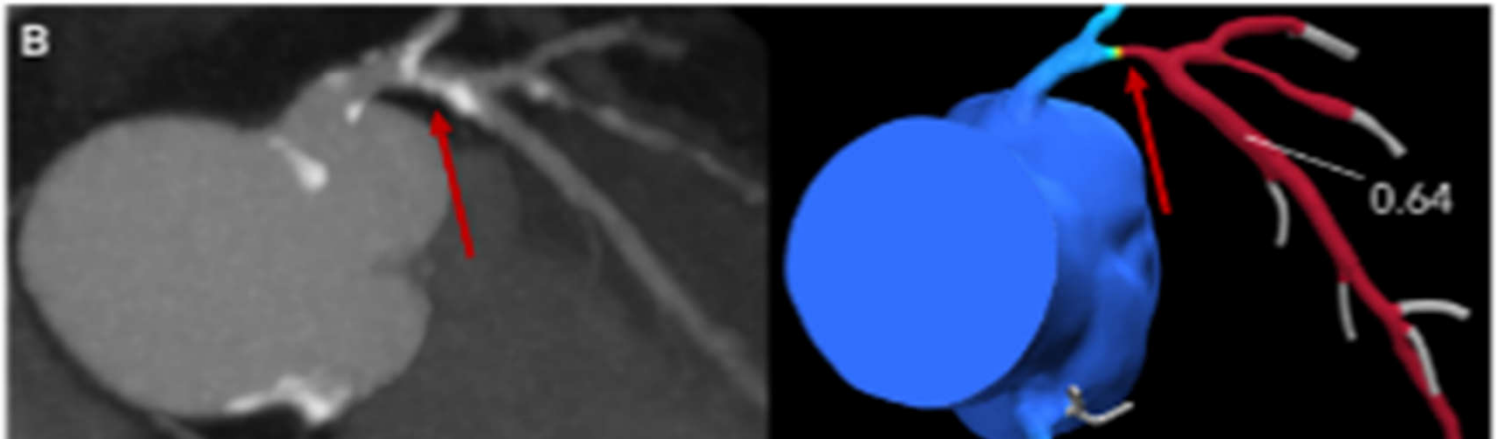


Figure 2: Coronary CT angiography (CTA) images (left side, **A** and **B**) and corresponding derived fractional flow reserve (FFR) (right side, **A** and **B**). The location 2 cm distal to stenosis is manually delineated and the coronary CTA–derived FFR (FFR_{CT}) value is registered. The lowest lesion-specific coronary CTA–derived FFR value is used to categorize participants, with **(A)** greater than 0.80 representing a normal value and **(B)** 0.80 or less representing an abnormal value.