Como planear o rastreio?

Identificação do período de contagiosidade

Quadro 15 – Identificação do período de contagio

Presença de sintomas	Laboratório	Radiologia	Período de contagiosidade
Sim	Exame direto positivo	Com ou sem cavitaçao	3 meses antes do inicio dos sintomas ou do primeiro achado consistente com a doença.
Sim	Exame direto negativo e cultural positivo	Com cavitação	3 meses antes do inicio dos sintomas ou do primeiro achado consistente com a doença.
Não	Exame direto negativo e exame cultural positivo	Sem cavitação	4 semanas antes do resultado do exame cultural

Identificação dos contactos em risco

No momento do diagnóstico, devem ser identificadas todas as pessoas consideradas como contactos próximos do doente. São definidos como contactos próximos as pessoas com 8 ou mais horas cumulativas de contacto (durante o período de contagiosidade), nos casos em que o doente tem baciloscopia positiva, ou com 40 ou mais horas cumulativas de contacto (durante o período de contagiosidade) nos casos em que o doente tem baciloscopia negativa e cultura positiva para MT.

Numa primeira fase, que não deve ultrapassar os 15 dias após o diagnóstico do caso de doença, devem ser rastreados todos os contactos próximos, assim como aqueles que, tendo apenas contacto esporádico com o caso, apresentem algum estado de imunodepressão que os coloque em risco acrescido de desenvolver doença (crianças com menos de 6 anos de idade, doentes com medicação imunossupressora ou infeção VIH).

Quando alargar o rastreio?

Deve-se alargar o rastreio para contactos esporádicos, sempre que sejam diagnosticados casos adicionais de doença no âmbito do primeiro rastreio, ou haja evidência de transmissão recente traduzida por:

- Proporção dos contactos com conversão tuberculínica ou IGRA positivo;
- Existência de crianças com menos de 6 anos infectadas ou doentes;
- Existência de outros contactos doentes;
- Prevalência maior que o esperado de infectados entre os contactos rastreados.

Interpretação dos testes de rastreio e respetiva decisão clínica

O indivíduo imunocompetente

O primeiro passo na estratégia de rastreio de contactos de TB é a exclusão de doença ativa[1], através de inquérito de sintomas e radiografia torácica.

Posteriormente, prossegue-se para a investigação de TB infecção latente. Dado não existir ainda um teste que consiga definir claramente os indivíduos com infecção latente por *Mycobacterium tuberculosis* e que vão beneficiar do tratamento, são utilizados testes que avaliam a resposta imunológica adaptativa aos antigénios micobacterianos[2]. São eles o TST[3] e IGRA[4]. Ambos apresentam vantagens e limitações, salientando-se a elevada sensibilidade do TST em indivíduos imunocompetentes[3] e a elevada especificidade dos testes IGRA[4]. Desta forma, a utilização dos 2 testes numa estratégia de rastreio é recomendada pela maioria dos autores[2].

Na figura 2, é apresentado o fluxograma de rastreio de contactos de TB em indivíduos imunocompetentes e respectiva interpretação dos testes utilizados. Sendo a infecção por TB mediada por um mecanismo de hipersensibilidade retardada, é necessária uma reavaliação após um período janela de 8-12 semanas para a excluir com segurança[1].

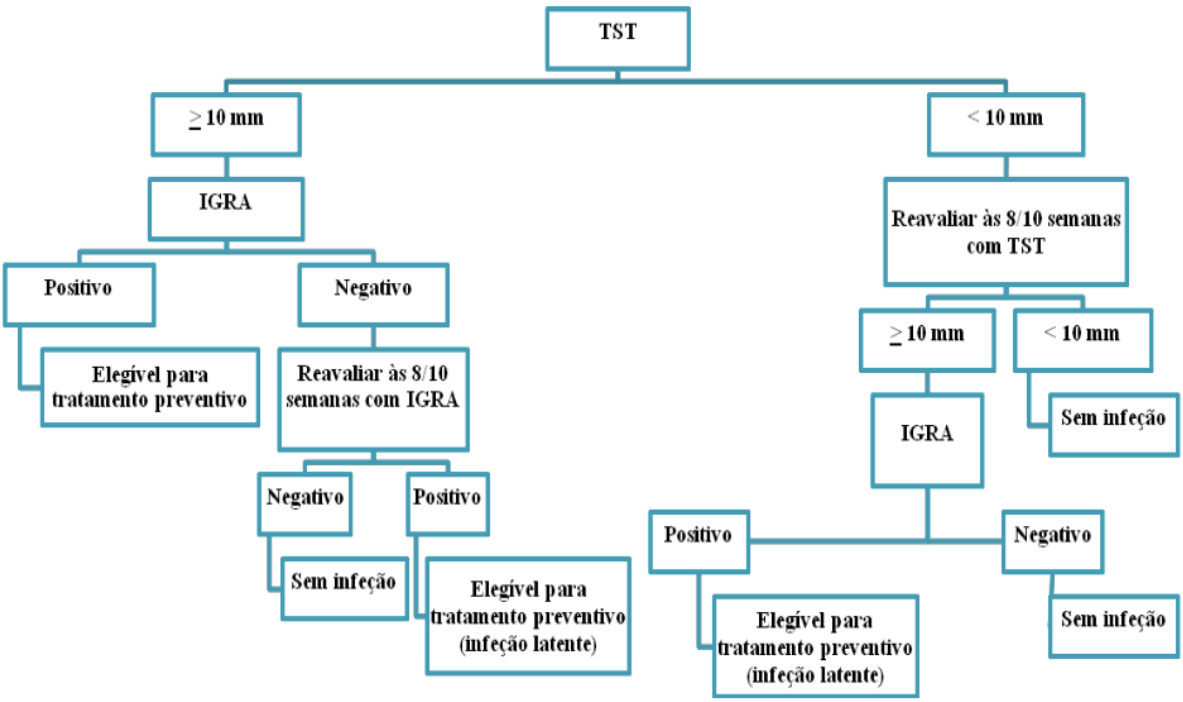

Figura 2 – Fluxograma para interpretação do TST e IGRA em individuos adultos imunocompetentes

O indivíduo imunocomprometido

O doente imunocomprometido (pela baixa idade, infecção por VIH, sob terapêutica imunossupressora e/ou sob corticoterapia prolongada em doses elevadas) se infectado pelo MT, apresenta alto risco de progredir para doença ativa, particularmente nos casos por infecção por VIH ou sob terapêutica imunossupressora. Por isso, devem ter prioridade na realização do rastreio. O rastreio é condicionado pela debilidade dos sintomas e das alterações radiográficas presentes e pelos resultados falsamente negativos na detecção de infecção latente (figura 3).

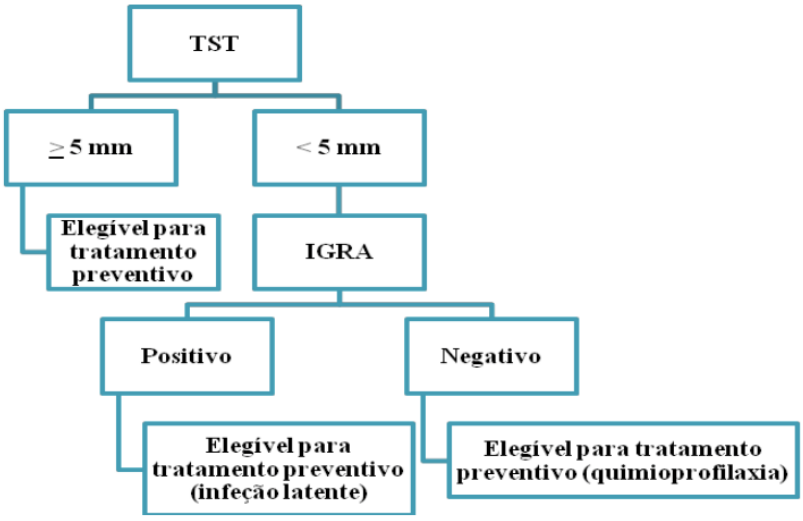

Figura 3 – Fluxograma para interpretação do TST e IGRA em indivíduos imunocomprometidos

Os esquemas de tratamento para infecção latente são os utilizados para os imunocompetentes (quadro 16).

Para além disso, durante o rastreio de contactos, devem iniciar quimioprofilaxia imediatamente após exclusão de doença.

Quadro 16 – Esquemas disponíveis para tratamento de TB infeção latente

Esquemas (meses)	Dosagem	Comentários
6/9 H *	Crianças:10mg/Kg (max: 300mg) Adultos: 5 mg/Kg (max: 300 mg)	Esquema preferencial em qualquer dos grupos. Pode ser necessário associar Piridoxina.
4R	Crianças:10-20 mg/Kg (max 600 mg) Adultos: 10 mg/Kg (max 600 mg)	Recomendado na toxicidade/ intolerância ou resistência à isoniazida.
3HR	Crianças:10-20 mg/Kg (max 600 mg) Adultos: 10 mg/Kg (max 600 mg)	Recomendado na má adesão ao tratamento

*6H é o esquema recomendado nos imunocompetentes; o esquema 9H está recomendado para imunocomprometidos

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2. Rastreio do doente candidato a Terapêutica Biológica

A terapêutica biológica tem vindo a ser usada de forma crescente nas doenças inflamatórias crónicas. Estes fármacos estão relacionados com um risco aumentado de TB (dependendo do contexto clínico e do fármaco utilizado). O factor de necrose tumoral alfa (TNF-) é fundamental na defesa imunológica contra o MT, especialmente na formação e manutenção dos granulomas, pelo que a inibição deste (e consequentemente, da rede de quimiocinas reguladas por ele) aumenta a suscetibilidade ao desenvolvimento de TB doença. A TB doença no contexto de terapêutica anti-TNF- pode resultar da reativação de infecção latente ou de infeção durante o tratamento. A terapêutica preventiva nos doentes com TB latente reduz significativamente a incidência de TB doença, pelo que o rastreio sistemático destes doentes é fundamental. O rastreio anual, assim como a pesquisa de exposição a casos de TB durante o tratamento poderão reduzir os casos de doença que decorrem devido a novas infeções.

Quem rastrear?

- Todos os pacientes com doenças autoimunes candidatos a medicação biológica

Quando rastrear?

- Antes do início da terapêutica biológica e preferencialmente à data do diagnóstico da doença, antes do início de qualquer terapêutica imunossupressora.
- Anualmente, se o primeiro rastreio foi negativo e se mantém terapêutica biológica
- Sempre que ocorrer exposição a caso de TB

Como rastrear?

Exclusão de doença ativa

- Inquérito de sintomas
- Radiografia do tórax (TAC se adequado)
- Na Doença de Crohn, exame micobacteriológico direto e cultural ou teste de amplificação de ácidos nucleicos de biópsias endoscópicas.

Rastreio de infeção latente

O rastreio de infeção latente é feito com utilização de TST e IGRA (figura 1 e 2).

Quem é elegível para tratamento preventivo?

A presença de pelo menos um dos seguintes parâmetros é indicação para tratamento de tuberculose latente, independentemente da idade, se o doente é candidato a medicação biológica:

- Factores de risco epidemiológicos de TB*
- Alterações radiológicas compatíveis com TB pregressa não tratada
- TST ≥ 10mm no imunocompetente ou ≥ 5mm no imunodeprimido
- IGRA positivo

* História de exposição a TB, TB prévia não tratada ou incorretamente tratada, imigrantes de áreas com prevalência elevada de TB, residentes em áreas com elevada incidência de TB, comorbilidades associadas com risco aumentado de TB, atividades profissionais com risco de exposição a TB, viagens a países endémicos.

Que regime terapêutico utilizar?

O mesmo que nos imunocompetentes, dando-se preferência ao esquema de 9 meses de isoniazida, que confere maior eficácia preventiva. O esquema de 3 meses de HR é reservado para situações onde há problemas com a adesão ao tratamento os 4 meses de rifampicina para os casos com efeitos adversos associados à isoniazida ou exposição a doente com resistência à isoniazida.

Quando pode o doente iniciar medicação biológica?

Ao fim de 4 semanas de terapêutica preventiva.

Como fazer o *follow-up* dos doentes sob terapêutica biológica?

- Rastreio anual em doentes sob terapêutica biológica com rastreio inicial negativo
- Pesquisa em cada consulta de exposição a doentes com tuberculose
- Pesquisa em cada consulta de sintomas sugestivos de tuberculose – tosse, expetoração, emagrecimento, sudorese, astenia.

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3. Rastreio do doente VIH positivo

A infeção pelo VIH confere maior risco para progressão para doença (risco anual de 10-100 casos de tuberculose/100 pessoasano) nos indivíduos infetados pelo Mycobacterium tuberculosis. Da mesma forma que todos os indivíduos com diagnóstico de tuberculose devem fazer rastreio da infeção pelo VIH, todos os indivíduos com infeção pelo VIH devem ser rastreados para tuberculose. A identificação e o tratamento da infeção latente por MT nesta população permite reduzir o risco de progressão para doença e traz, por isso, benefícios quer ao nível individual quer do ponto de vista de saúde pública.

Como rastrear?

- Rastreio de infeção latente é feito com recurso ao teste tuberculínico e teste IGRA.
- É fundamental a exclusão de doença ativa através do inquérito de sintomas e radiografia do tórax (TAC se adequado).

Quando rastrear? Em que situações o rastreio deve ser repetido e com que frequência?

- Tão precocemente quanto possível, após o diagnóstico da infeção pelo VIH.
- Se o 1º rastreio tiver sido efetuado com contagem de linfócitos TCD4+<200/mm3 deverá ser repetido, assim que linfócitos T CD4+>200/mm3 (idealmente > 400/mm3).
- rastreio deve ser repetido anualmente nos doentes com rastreio inicial negativo ou antes se ocorrer exposição a doente com tuberculose.
- Em cada consulta de seguimento destes doentes, deve ser inquirida: história de exposição a doentes com tuberculose; sintomas sugestivos de tuberculose (tosse, expetoração, emagrecimento, sudorese, astenia).

Critérios para início de tratamento preventivo? (pelo menos 1)

- TST > 5mm ou IGRA Positivo
- Radiografia pulmonar com sequelas e sem história de tratamento adequado
- História prévia de tuberculose sem tratamento completo
- História de contacto recente com caso de tuberculose (independentemente de resultado de TST ou IGRA)

Estes critérios só se aplicam se o doente não apresentar sintomatologia ou radiografia sugestiva de tuberculose ativa!

Porquê fazer tratamento preventivo?

- A terapêutica anti-retrovírica por si só, e ao melhorar a resposta imunológica, reduz a probabilidade de progressão de infeção latente por MT para doença ativa;
- Tratamento da infeção latente por MT com isoniazida, associado a terapêutica anti-retrovírica, tem um efeito adicional na redução da probabilidade de progressão de infeção latente por MT para doença ativa.

Quando iniciar tratamento para infeção latente por MT no doente infetado pelo VIH que não está sob TAR?

Uma das preocupações do clinico é que antes de iniciar tratamento preventivo é fundamental a exclusão de doença ativa, o que pode ser difícil num doente com imunossupressão avançada pela inespecifidade da clinica e radiologia.

Por outro lado, após o início de TAR, uma tuberculose subclínica pode tornar-se clinicamente evidente, no contexto de uma melhoria da resposta imunológica (i.e. síndrome de reconstituição imunológica que geralmente ocorre nos primeiros 3 meses após início de ARV);

Assim, de forma a reduzir o risco de erro, propõe-se uma abordagem faseada:

1. Perante um doente infetado pelo VIH, com critérios para iniciar ARV, aparentemente sem tuberculose ativa (sem sintomas ou radiologia sugestiva), com critérios para inicio de tratamento preventivo, a ARV deve ser considerar como intervenção prioritária.
2. O tratamento de infeção latente por MT deve ser protelada para cerca de 3 meses após o inicio de ARV.

Os doentes em tratamento preventivo devem ter vigilância clinica e analítica mensal.

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1. Micobactérias Não-tuberculosas

As MNT são as micobactérias que não pertencem ao *Mycobacterium tuberculosis* complex ou *Mycobacterium leprae*. Estão descritas mais de 160 espécies de MNT[1], embora a importância clínica da grande maioria seja incerta[2]. São classificadas fenotipicamente em micobactérias de crescimento rápido (formação de colónias ≤ 7 dias) e de crescimento lento (formação de colónias > 7 dias) (tabela 2).

A doença por MNT resulta da interacção MNT-hospedeiro-ambiente. É mais prevalente em doentes com patologia estrutural (bronquiectasias, por exemplo) e em imunodeprimidos. O diagnóstico de doença implica a presença de semiologia compatível, alterações imagiológicas e isolamentos microbiológicos (Quadro 17).

Quadro 17 - Critérios diagnósticos de doença pulmonar por MNT

Semiologia	Imagiologia	Microbiologia
Tosse crónica ou recorrente Expetoração (muco)purulenta Hemoptises Dispneia Toracalgia Febre Fadiga Perda ponderal Mal-estar geral	**Doença Fibrocavitária** Cavidades de parede fina nos lobos superiores Envolvimento pleural **Doença Nodular/Bronquiectásica**[a] Padrão *tree-in-bud* (*clusters* de nódulos <5mm) Padrão de *vidro despolido* Envolvimentos dos lobos médio/língula e inferiores Bronquiectasias	Culturas positivas em pelo menos 2 amostras distintas de expectoração[b] **ou** Cultura positiva de um lavado brônquico[c] **ou** Biópsia transbrônquica ou outra pulmonar com características histológicas compatíveis (granulomas ou BAAR[d]) + cultura positiva para MNT na amostra ou cultura positiva em lavado brônquico

[a] Frequentemente causada por MAC em mulheres pós-menopausa com escoliose, *pectus excavatum* e prolapso da válvula mitral.
[b] As amostras devem obrigatoriamente ser colhidas em dias diferentes.
[c] Para doença nodular/bronquiectásica e *Mycobacterium avium complex*. Para as outras MNT deve ser consultado um especialista.
[d] BAAR – bacilos álcool-ácido resistentes.

O tratamento de doença por MNT (Quadro 18) é prolongado, devendo ser mantido por 12 meses após a conversão das culturas[3–5]. A falência do tratamento implica a não melhoria clínica, imagiológica e microbiológica após 6 meses ou a não negativação das culturas após 12 meses de tratamento[3]. Uma vez que a cura pode não ser um *outcome* tangível, outras metas de sucesso terapêutico podem ser definidas como a melhoria sintomática, imagiológica e a negativação de culturas no curto prazo[3].

A cirurgia deve ser reservada para casos de doença resistente ao tratamento instituído e em que seja possível uma ressecção anatómica.

O seguimento implica a vigilância clínica e microbiológica mensal durante todo o tratamento e um *follow-up* mínimo de 2 anos após tratamento.

Quadro 18 – Esquemas de tratamento das MNT mais frequentemente isoladas na Europa

MNT	Especificidade	Esquema Terapêutico[3-5]
M avium (MAC)	Doença nodular/ bronquiectásica[a]	Macrólido[b] + R (600mg) + E (25mg/Kg) ou Macrólido[b] + E (25mg/Kg) (se intolerância a rifamicinas[4])
	Doença fibrocavitária[c]	Macrólido[b] + R (10mg/Kg)[d] ou Rifabutina (150-300mg) + E (15mg/Kg) + S ou Amicacina (8-10mg/Kg) (3x/semana nos primeiros 3 meses)
	MAC resistente a macrólidos	R(10mg/Kg)[d] ou Rifabutina (150-300mg) + E (25mg/Kg)[e] + H (300mg) Referenciar a um especialista na área
M kansasii	Sensível a Rifampicina	R (10mg/Kg)[d] + E (15mg/Kg) + H (5mg/Kg) + Piridoxina (50mg/dia) ou R (10mg/Kg)[d] + E (15mg/Kg) + Macrólido[b] ou Moxifloxacina (400mg id)[4]
	Resistente a Rifampicina	3 fármacos com susceptibilidade *in vitro* (macrólido[b], moxifloxacina, etambutol, sulfametoxazole, estreptomicina)
M xenopi	-	Macrólido[b] + R (10mg/Kg)[d] ou Rifabutina (150-300mg) + H + E (15mg/Kg) ± Estreptomicina ou Amicacina (8-10mg/Kg) (depende da gravidade)
M abscessus	-	Macrólido[b] + Amicacina (10-15mg/Kg)[i] ou Imipenem (500mg/2-4id) Outros fármacos: Linezolide, Tigeciclina, Telitromicina
M chelonae	-	Claritromicina (500mg 2id) + 2º fármaco de acordo com TSA (tobramicina, linezolide, imipenem, amicacina, clofazimina, doxiciclina, ciprofloxacina)
M fortuitum	-	2 fármacos de acordo com TSA (amicacina, ciprofloxacina, ofloxacina, sulfonamidas, cefoxitina, imipenem, claritromicina[i], doxiciclina)

Nota: estes esquemas devem ser discutidos com especialista na área

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2. Linfadenite por Bacillus Calmette-Guérin (BCGite)

A vacina BCG é utilizada em vários países, reduzindo a probabilidade de formas disseminadas de tuberculose e de meningite tuberculosa na criança. Em Portugal, a vacina é administrada a todos os recém-nascidos com um peso ao nascimento superior a 2000g e não imunocomprometidos. A administração de BCG é efetuada por injeção intradérmica, induzindo uma reação primária local, com a formação de uma indução de cerca de 5 mm no local de injeção. A indução evolui então para uma pústula com consequente ulceração 2 a 3 semanas após a vacinação. Cerca de 4 a 6 semanas depois, ocorre drenagem do conteúdo da lesão ulcerada, formação de crosta e, ao fim de 10 a 12 semanas verifica-se a resolução da lesão com a formação de cicatriz. O envolvimento ganglionar regional ou local ocorre de forma subclínica e regride espontaneamente.[1,2]

A incidência de reações adversas à acina BCG ocorre até 0,1 a 0,5 por 1000 vacinas e parecem estar relacionadas com a via e a técnica de administração, a idade e estado imunológico do vacinado e a qualidade, estirpe e dose de vacina administrada.[3]

O termo linfadenite por BCG ou BCGite deve ser aplicado quando o aumento dos gânglios é suficientemente grande para ser facilmente palpável. A grande maioria ocorre nos primeiros 6 meses, mas pode aparecer até aos 2 anos. Em 95% dos casos estão envolvidos os gânglios axilares ipsilaterais, embora os gânglios supraclaviculares e cervicais ipsilaterais também possam estar envolvidos.[1]

Existem duas formas de BCGite: a forma não supurativa (forma simples), que resolve espontaneamente em semanas ou meses e a forma supurativa que se caracteriza por rubor, edema e flutuação. Os gânglios supurados podem conduzir a drenagem persistente e formação de fístula. Se não tratados, a cicatrização pode demorar vários meses.[3]

O diagnóstico de BCGite é clínico, pelo que não são necessários exames auxiliares de diagnóstico (quadro 19).[1,3]

A administração de antibióticos (ex. eritromicina) ou antituberculosos (ex. isoniazida e rifampicina) não reduz o risco de supuração nem acelera a resolução, pelo que se recomenda apenas vigilância clinica nas formas não supurativas.[1,3]

O tratamento cirúrgico mais adequado para a adenite supurada não é consensual. A aspiração por agulha tem sido defendida como uma maneira de evitar a supuração e a drenagem prolongada.[1,3,4] É considerada uma opção mais segura comparativamente à excisão total uma vez que esta necessita de anestesia geral em crianças pequenas.[3]

A excisão cirúrgica é, para alguns autores, o tratamento de escolha na forma supurada, considerando o risco de recorrência e supuração após a aspiração.[4,5] No entanto, dados os riscos cirúrgicos da excisão

e tendo em conta os bons resultados obtidos com a aspiração, alguns autores defendem que a excisão deve ser reservada para situações específicas: gânglios com diâmetro superior a 3 cm, se gânglios multiloculados, se fistulização e se surgem nos primeiros 2 meses após a vacinação. A incisão simples e drenagem não são recomendadas porque resultam na drenagem persistente com um longo período de cicatrização (Figura 4). [1,3,4]

Quadro 19 - Características clínicas sugestivas de BCGite

Características clínicas sugestivas de BCGite
História de vacinação por BCG no braço ipsilateral.
Início 2 a 4 meses após vacinação (pode variar entre 2 semanas e 6 meses).
Ausência de febre ou outros sintomas constitucionais.
Ausência ou tensão mínima local.
Envolvimento dos gânglios axilares ipsilaterais (95% dos casos), embora possa haver envolvimento dos gânglios supraclaviculares ou cervicais.
Apenas 1 ou 2 gânglios estão aumentados na maioria dos casos.

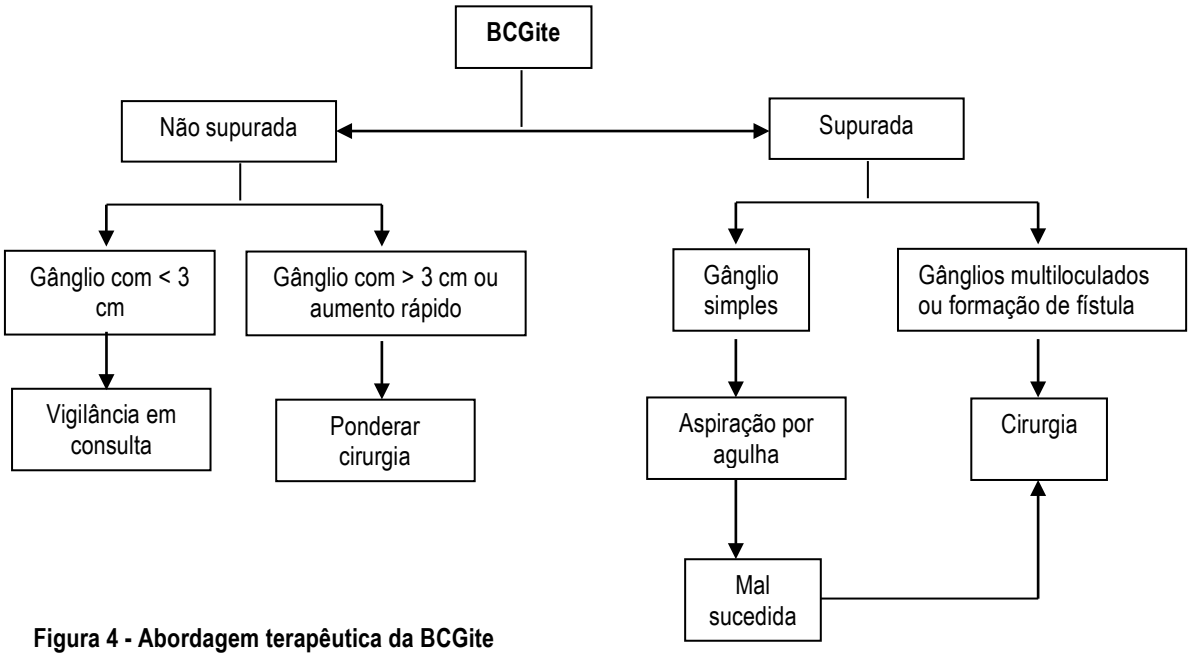

Figura 4 - Abordagem terapêutica da BCGite

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ORIENTAÇÃO

NÚMERO: 008/2017
DATA: 17/05/2017

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ASSUNTO:	Malária ou Paludismo
PALAVRAS-CHAVE:	Malária; vetores; mosquito Anopheles; *Plasmodium;* viajantes
PARA:	Sistema de Saúde
CONTACTOS:	DGS: dspdps@dgs.min-saude.pt

Nos termos da alínea a) do nº 2 do artigo 2º do Decreto Regulamentar nº 14/2012, de 26 de janeiro, emite-se a Orientação seguinte:

ORIENTAÇÃO

Considerando que, em Portugal, entre 2013 e 2015, foi diagnosticado um número crescente de casos de malária importados[1], há que reforçar a necessidade dos profissionais de saúde estarem preparados para o eventual aparecimento de novos casos, de forma a tornar possível o diagnóstico e o tratamento precoce dos doentes, evitando, assim, a evolução para malária grave, associada a mortalidade elevada.

1. Definição de caso[2]

Critérios clínicos	Critérios laboratoriais	Critérios epidemiológicos
Pessoa com febre ou antecedentes de febre	Pessoa com pelo menos um dos três critérios seguintes: – Demonstração da presença de *Plasmodium* spp. por microscopia ótica, em esfregaço sanguíneo e ou gota espessa; – Deteção de antigénios de *Plasmodium* spp.[3] – Deteção de ácido nucleico de *Plasmodium* spp.[4] Deve ser realizada, se possível, a identificação até à espécie de *Plasmodium.*	Não aplicável
Classificação de caso		
Caso possível Não aplicável **Caso provável** Não aplicável **Caso confirmado** Pessoa que preenche os critérios clínicos e um dos três critérios laboratoriais		

[1] https://www.dgs.pt/portal-da-estatistica-da-saude/diretorio-de-informacao/diretorio-de-informacao/por-instituicao.aspx
[2] https://dre.pt/application/file/a/105580101
[3] Por Teste Rápido de Diagnóstico.
[4] No sangue.

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2. Características clínicas[5]

O período de incubação após a picada do mosquito infetante depende da espécie do *Plasmodium* e do estado imunológico da pessoa infetada. Por *Plasmodium falciparum* e por *Plasmodium malariae* é no mínimo de cerca de 7 dias, por *Plasmodium vivax* e por *Plasmodium ovale* é no mínimo de cerca de 8 dias e por *Plasmodium knowlesi* o período de incubação ainda não está bem definido.

O período de incubação máximo é menor na infeção por *P. falciparum*, semanas, alguns meses, muito raramente pode ir até um ano. Na infeção por *P. vivax* e por *P. ovale* é mais prolongado, podendo chegar aos 3-5 anos. Na infeção por *P. malariae* não há limite temporal, havendo casos bem documentados com incubação de dezenas de anos. Quanto à infeção por *P. knowlesi o* limite máximo de incubação não está, ainda estipulado.

No caso de infeção por transfusão de sangue o período de incubação habitualmente é de poucas semanas, mas há casos documentados de vários anos.

O quadro clínico da malária é, em termos gerais, caraterizado por febre, calafrios, mialgias e artralgias, cefaleias, podendo evoluir com diarreia e vómitos. Além das características clinicas descritas, a esplenomegália, anemia, icterícia e trombocitopenia podem surgir passados alguns dias.

As complicações são mais frequentes na infeção por *P. falciparum* e por *P. knowlesi*. De entre as complicações, a forma central designada por malária cerebral é a mais preocupante. Caracteriza-se por: obnubilação, ou coma, convulsões, sinais focais, anemia grave, icterícia, falência renal, falência hepática, hipoglicémia, Síndrome de Dificuldade Respiratória Aguda, acidose metabólica e alterações da coagulação, podendo evoluir para coagulação intravascular disseminada, hipotensão, choque e morte.

O quadro clínico da malária por *P. vivax*, *P. ovale* e *P. malariae* inclui mal-estar e febre durante vários dias, seguido de calafrios, aumento súbito da temperatura, cefaleias e náuseas. Após um período de apirexia, surgem episódios cíclicos de calafrios, febre e sudorese, em dias alternados ou a cada três dias (febre terçã e febre quartã), em função da sincronia na multiplicação dos parasitas nos eritrócitos. A infeção primária não tratada pode durar de uma semana a um mês, ou mais, e ser acompanhada por prostração, anemia e esplenomegália.

As crianças <5 anos de idade, grávidas, idosos, viajantes, principalmente os que não fazem profilaxia, doentes e imunodeprimidos, entre os quais indivíduos com VIH/Sida, apresentam risco mais elevado de contrair malária e de poder desenvolver doença grave.

[5] Heymann, D. Control of Communicable Diseases Manual. American Public Health Association, 19th Edition, 2008; Jaime Nina. 2014. Malária. *in* F Maltez & A Almeida (Ed.) História das Doenças Infecciosas, pp 141-195. Lisboa, addsolutions; B Singha & C Daneshyarb. 2013. Human Infections and Detection of *Plasmodium knowlesi*. Clin Microbiol Rev 26(2):165-184.

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A malária deve sempre ser considerada uma emergência médica. Principalmente nas infeções por *P. falciparum,* o doente deve ser referenciado para o Hospital onde o diagnóstico e tratamento corretos possam ser rapidamente estabelecidos.

3. Diagnóstico laboratorial[6]

A metodologia laboratorial de referência inclui a observação direta do esfregaço sanguíneo e gota espessa em lâminas coradas com Giemsa que permite a identificação e diferenciação da espécie de *Plasmodium,* os estadios do ciclo de vida e a quantificação da parasitémia.

O diagnóstico laboratorial deve ser disponibilizado em poucas horas e inclui:

- Demonstração da presença de *Plasmodium* spp. por microscopia ótica, em esfregaço sanguíneo e/ou gota espessa;
- Deteção de antigénios de *Plasmodium* spp;
- Deteção de ácido nucleico de *Plasmodium* spp. no sangue.

4. Gestão de casos e tratamento

Perante um doente com quadro compatível de malária[7] é necessário recolher produtos biológicos para diagnóstico rápido e iniciar terapêutica adequada. O diagnóstico precoce e o tratamento imediato são os elementos básicos do controlo da doença.

Os hospitais do Serviço Nacional de Saúde devem ter, obrigatoriamente, em *stock*, medicação disponível para o tratamento das formas graves de malária.

No caso de tratamento em ambulatório, a primeira toma de antimalárico deve ser feita, sempre que possível, antes da alta para verificação da tolerância. O doente só deverá ter alta depois de garantida a existência de fármaco para continuar o tratamento sem interrupção e programado o seguimento. No caso de tratamento em ambulatório, o que só deverá ser prescrito por médicos com experiência no tratamento da malária, a monitorização diária do doente é recomendada.

O tipo e duração do tratamento depende de[8]:

- Espécie de plasmódio identificada;
- Previsível padrão de resistências do parasita;

[6] http://repositorio.insa.pt/bitstream/10400.18/3697/1/Boletim_Epidemiologico_Observacoes_N15_2016_artigo6.pdf
[7] Viajante que regressou de áreas endémicas, que apresente sintomas sugestivos de infeção por malária (febre, calafrios, dores de cabeça, dores musculares e mal-estar), até 6 meses após o regresso e que não cumpriu adequadamente a quimioprofilaxia.
[8] http://www.nhs.uk/conditions/Malaria/Pages/Introduction.aspx

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- Forma de apresentação clínica, nomeadamente gravidade dos sintomas;
- Quimioprofilaxia prévia contra a malária e do antimalárico realizado;
- Gravidez.

No caso de malária por *P. falciparum*, o doente deve ser tratado o mais rapidamente possível, no máximo dentro de 24 horas após o início dos sintomas. Caso contrário, a situação clínica pode evoluir para doença grave, levando muitas vezes à morte. Se o laboratório não fornecer o diagnóstico da espécie de *Plasmodium* infetante, o clínico deverá considerar que este é *P. falciparum* e atuar em conformidade.

O clínico que diagnostica um caso de malária deve de imediato proceder à respetiva notificação no Sistema Nacional de Vigilância Epidemiológica (SINAVE) através de https://sinave.min-saude.pt/SiVDoT/Login.aspx.

5. Recomendações para viajantes[9,10]

As recomendações para viajantes baseiam-se na combinação das medidas de prevenção da malária[11] e incluem:

- Verificar previamente se o País de destino tem transmissão de malária. Esta informação está disponível em http://www.who.int/malaria/publications/country-profiles/en/. É necessário ter em conta que o risco de malária é variável em função da região de destino, dependendo ainda da época do ano, da densidade do vetor e da prevalência da infeção.
- Marcar Consulta do Viajante[12] ou com o Médico Assistente, pelo menos 4 semanas antes da partida.
- Realizar quimioprofilaxia da malária, se aplicável e de acordo com as indicações do médico.
- Adotar medidas de proteção individual contra a picada de mosquitos:
    - Evitar estar ao ar livre entre o anoitecer e o amanhecer. A transmissão da malária ocorre principalmente neste período devido aos hábitos alimentares noturnos da maioria dos mosquitos *Anopheles*. No entanto, outros mosquitos podem picar durante o dia e transmitir outras doenças. Portanto, a proteção individual contra a picada dos mosquitos deve ser praticada ao longo de todo o dia.

[9] https://www.cdc.gov/malaria/travelers/
[10] http://www.fitfortravel.scot.nhs.uk/advice/malaria.aspx
[11] Várias vacinas contra a malária estão em desenvolvimento, nenhuma está atualmente disponível.
[12] https://www.sns.gov.pt/home/consulta-de-saude-do-viajante-2/

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- Aplicar repelentes em adultos e crianças, de acordo com as instruções do fabricante. Se utilizar protetor solar ou qualquer outro creme e repelente, deverá aplicar primeiro o protetor solar ou o outro creme e depois o repelente.
- Proteger as crianças em carrinhos de bebé e berços com redes mosquiteiras de preferência impregnadas com inseticida piretróide.
- Optar por alojamento com ar condicionado ou, em alternativa, utilizar redes mosquiteiras nas camas.
- Utilizar vestuário preferencialmente largo, de cores claras, fibras naturais e que diminua a exposição corporal à picada dos mosquitos (camisas de manga comprida, calças e calçado fechado). Os mosquitos podem picar através de roupas finas, devendo pulverizar ou aplicar repelente nas roupas. Um inseticida piretróide pode ser aplicado nas roupas e calçado.

- As grávidas devem evitar viajar para áreas onde existe transmissão de malária, uma vez que a sua infeção pode ser mais grave. Se a viagem for inadiável, devem consultar o médico assistente e adotar medidas preventivas.
- Viajantes que regressem de áreas endémicas e que apresentem sintomas sugestivos de infeção por malária (febre, calafrios, dores de cabeça, dores musculares e mal-estar), até 6 meses após o regresso, devem contactar a Saúde 24 (808 24 24 24) ou consultar o médico assistente, logo que possível, referindo a viagem.

5.1. Quimioprofilaxia

Embora a malária possa ser letal, a doença e a morte são em grande parte evitáveis. Atualmente, não existe vacina disponível que ofereça proteção contra a malária, pelo que a quimioprofilaxia é muito importante para reduzir a probabilidade de contrair a doença.

Quando devidamente tomados os antimaláricos têm uma eficácia acima de 90 % na prevenção da doença; no entanto, para redução do risco de infeção o seu uso deve sempre ser complementado com medidas de proteção individual contra a picada de mosquitos[13].

Os viajantes que se desloquem para países endémicos podem ter indicação para efetuar quimioprofilaxia devendo ser previamente avaliados em Consulta do Viajante ou pelo médico assistente.

A escolha do fármaco utilizado depende do destino, da duração de permanência, do padrão de resistência do parasita, do nível e da sazonalidade da transmissão, da idade, das atividades a realizar, dos antecedentes pessoais, do estado de saúde e de eventual gravidez.

[13] http://www.nhs.uk/Conditions/Malaria/Pages/Prevention.aspx

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Relativamente à quimioprofilaxia:

- Deve ter início, antes da chegada à área de risco, de acordo com as orientações fornecidas na Consulta do Viajante ou pelo médico assistente;
- Deve ser cumprida de acordo com a prescrição médica, reforçando que após o regresso, é extremamente importante continuar a cumprir a terapêutica, a qual tem em conta o ciclo de vida e a espécie de *Plasmodium*.

6. Fundamentação

A malária é uma doença infeciosa causada pelo parasita do género *Plasmodium* transmitido ao ser humano através da picada da fêmea de mosquitos *Anopheles*. Existem cinco espécies de parasita que causam malária no ser humano: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale, Plasmodium malariae e Plasmodium knowlesi*. Esta última é responsável por malária em macacos no sudeste asiático e foi recentemente identificada como sendo patogénica no Homem.

As espécies *P. falciparum* e *P. vivax* representam a maior ameaça a nível mundial dado que[14]:

- *P. falciparum* é o agente da malária com maior prevalência no continente africano e é responsável pela maioria das mortes atribuídas a malária, a nível global.
- *P. vivax* é o parasita mais prevalente nas restantes regiões onde ocorre malária com exceção da África subsariana.

Ocasionalmente, a transmissão também pode ocorrer por transfusão de sangue, transplante de órgãos, partilha de agulhas ou por transmissão vertical (da mãe para o feto).

A Organização Mundial da Saúde (OMS) estima que, em 2015, tenham sido identificados 212 milhões de casos de malária a nível mundial e que cerca de 429.000 pessoas tenham morrido da doença, principalmente crianças <5 anos de idade, devido a baixa imunidade[15].

Embora a prevalência da malária em termos globais tenha diminuído, muitas áreas continuam endémicas e a utilização de medidas preventivas continuam inadequadas ou insuficientes. A malária constitui um grave problema de saúde pública na maioria dos países da África Subsariana. A transmissão da malária ocorre também em áreas da América Central e do Sul, Ásia, Europa Oriental e Pacífico Sul.

Em Portugal, os últimos casos de malária autóctone foram diagnosticados em 1959. Desde então, só têm sido identificados casos importados de países tropicais onde a doença é endémica. Entre 2013 e 2015, verificou-se um aumento do número de casos (cerca de 150 casos/ano).

[14] http://www.who.int/mediacentre/factsheets/fs094/en/
[15] http://www.who.int/malaria/travellers/en/

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Por esta razão é da maior importância que os médicos estejam preparados para suspeitar de mais casos da doença de forma a permitir diagnóstico e terapêutica precoce.

Considerando o fenómeno do aquecimento global e do aumento do tráfego de pessoas e mercadorias, fatores que poderão contribuir para a reintrodução da malária na Europa, é absolutamente necessário reforçar a vigilância epidemiológica do vetor nos portos e aeroportos.

O Instituto Ricardo Jorge e a Direção-Geral da Saúde participam na vigilância epidemiológica da malária através da Rede de Vigilância de Vetores (REVIVE) nos portos e aeroportos.



Francisco George
Diretor-Geral da Saúde

A Direção-Geral da Saúde agradece aos profissionais que colaboraram na elaboração desta Orientação, incluindo:

- Grupo de trabalho das Doenças Transmissíveis
- Instituto de Higiene e Medicina Tropical
- Instituto Ricardo Jorge

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DGS desde 1899 Direção-Geral da Saúde

NORMA
da Direção-Geral da Saúde

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NÚMERO: 006/2014
DATA: 08/05/2014
ATUALIZAÇÃO: 08/05/2015

ASSUNTO: Duração de Terapêutica Antibiótica

PALAVRAS-CHAVE: Terapêutica antibiótica, duração, resistência a antimicrobianos, pressão antibiótica

PARA: Médicos do Sistema de Saúde e Grupos de Coordenação Local do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos

CONTACTOS: Departamento da Qualidade na Saúde (dqs@dgs.pt)

Nos termos da alínea a) do nº 2 do artigo 2º do Decreto Regulamentar nº 14/2012, de 26 de janeiro, por proposta conjunta do Departamento da Qualidade na Saúde, do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos e da Ordem dos Médicos, a Direção-Geral da Saúde emite a seguinte:

NORMA

1. As infeções bacterianas devem, como regra geral, ser tratadas com cursos de terapêutica antibiótica não superiores a sete (7) dias. A evidência para utilização desta duração de terapêutica antibiótica está resumida no seguinte quadro:

Tipo de infeção	**Duração recomendada**	**Graus de Recomendação e Níveis de Evidência**
Vias Urinárias		
Pielonefrite	7 dias	IIa B [1,2]
Cistite não complicada	1-7 dias*	I A [1,3]
Cistite complicada	7 dias	IIa B [1]
Pulmão		
Pneumonia da comunidade	5-7 dias**	I A [4,5]
Pneumonia hospitalar	7 dias	I A [6,7]
Infeções intra-abdominais		
Com controlo adequado do foco	4-7 dias	I A [8]
Sem intervenção cirúrgica	7 dias	IIa C [8]
Bacteriemia primária		
Com controlo do foco	7 dias	I B [9]
Resolução clínica após retirada de cateter venoso central (CVC)	0-3 dias	IIb C [9]
Meningite		
Por *Neisseria meningitidis* ou *Haemophilus influenzae*	7 dias	I C [10]
Outros focos		
Pele e tecidos moles não complicados	3-7 dias	IIa B [11]
Amigdalite bacteriana	1 administração	I A [12,13]
Sinusite do adulto não recidivante	7 dias	I A [14]

* 3-7 dias em idade pediátrica ** 7 dias em idade pediátrica

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2. As infeções bacterianas agudas que necessitam de mais de sete (7) dias de terapêutica antibiótica são:

Tipo de infeção	**Duração recomendada**	**Graus de Recomendação e Níveis de Evidência**
Cistite ou pielonefrite complicada com resolução clínica lenta	10 dias	IIb B [2]
Prostatite	4-6 semanas	IIa C [2]
Pneumonia por *Legionella* spp	10-14 dias	I A [15]
Pneumonia por bacilos de Gram negativo não fermentadores	7-14 dias	IIa B [6]
Pneumonia a *Pneumocystis jiroveci*	21 dias	IIa B [15]
Pneumonia necrotizante	10-14 dias	IIa C [15]
Abcesso pulmonar	4-6 semanas	IIa C [15]
Empiema	2-6 semanas	IIb C [15]
Foco intra-abdominal persistente	10-14 dias	IIa B [8]
Colite pseudomembranosa	10 dias	I A [16-18]
Bacteriemia por *Staphylococcus aureus*	14-21 dias	I A [9,10]
Meningite por *Streptococcus pneumoniae*	10 dias	I C [10]
Meningite por bacilos de Gram negativo, *Streptococcus agalactiae* ou *Listeria spp*	14-21 dias	I C [10]
Abcesso cerebral	4-8 semanas	IIa B [10,20]
Osteomielite hematogénea	4-8 semanas	IIa B [21]
Artrite séptica	2-4 semanas	II A [22]
Artrite séptica em prótese	2-3 meses	II A [22,23]
Fasceíte necrotizante/gangrena gasosa	Variável*	I C [11]
Pericardite bacteriana	4 semanas	IIa C [24]
Endocardite não complicada de válvula nativa**	4 semanas	I A [24]
Pós-operatório de endocardite	2 semanas	I A [24,25]
Mediastinite	10-14 dias	IIIb C [26]
Febre tifoide	14 dias	I A [27]
Brucelose	6 semanas	I A [28]
Doença de Lyme	14-28 dias	I C [29]

*Duração da terapêutica fundamentada no processo clínico do utente

**Quando causada por *Streptococcus* do grupo *viridans* ou *S. bovis* com elevada sensibilidade à penicilina e sensíveis à gentamicina, a duração indicada para o tratamento com a associação dos dois fármacos é de duas semanas (IIA)[24].

3. Um médico do Grupo de Coordenação Local do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos, através da implementação de programa de apoio à prescrição antibiótica, conforme Despacho 15423/2013[28], deve utilizar esta Norma no sentido de assegurar a suspensão da terapêutica antibiótica, sempre que não houver confirmação de existência de infeção bacteriana.

4. Um médico do Grupo de Coordenação Local do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos, através da implementação de programa de apoio à prescrição

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antibiótica, conforme Despacho 15423/2013[30], deve utilizar esta Norma no sentido de limitar a duração da terapêutica antibiótica de acordo com o indicado nos enunciados normativos.

5. Qualquer exceção à presente Norma é fundamentada clinicamente, com registo no processo clínico.

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6.O instrumento de auditoria clínica

Instrumento de Auditoria Clínica da Norma " Duração de Terapêutica Antibiótica"				
Unidade: ----------				
Data: __/__/___ **Equipa Auditora**:				
1: Duração de Terapêutica Não Superior a Sete Dias				
A: Vias urinárias				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Pielonefrite (7 dias)				
Cistite não complicada (1 a 7 dias)				
Cistite não complicada (3 a 7 dias em idade pediátrica)				
Cistite complicada (7 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
B: Pulmão				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Pneumonia da comunidade (5 a 7 dias)				
Pneumonia da comunidade (7 dias em idade pediátrica)				
Pneumonia hospitalar (7 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
C: Infeções intra-abdominais				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Com controlo adequado do foco (4 a 7 dias)				
Sem intervenção cirúrgica (7 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
D: Bacteriemia Primária				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Com controlo do foco (7 dias)				
Resolução clínica após retirada de catéter venoso central (CVC) (0 a 3 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
E: Meningite				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Por *Neisseria meningitidis* ou *Haemophlilus influenza* (7 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
F : Outros focos				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Pele e tecidos moles não complicados (3 a 7 dias)				
Amigdalite bacteriana (1 administração)				
Sinusite do adulto não recidivante (7 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
2 : Duração de Terapêutica Superior a Sete Dias				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Cistite ou pielonefrite complicada com resolução clínica lenta (10 dias)				
Prostatite (4 - 6 semanas)				
Pneumonia por *Legionella* spp (10 14 dias)				
Pneumonia por bacilos de Gram negativo não fermentadores (7 - 14 dias)				
Pneumonia a *Pneumocystis jiroveci* (21 dias)				
Pneumonia necrotizante (10 - 14 dias)				
Abcesso pulmonar (4 - 6 semanas)				
Empiema (2 6 semanas)				
Foco intra-abdominal persistente (10 - 14 dias)				
Colite pseudomembranosa (10 dias)				
Bacteriemia por *Staphylococcus aureus* (14 - 21 dias)				
Meningite por *Streptococcus pneumoniae* (10 dias)				
Meningite por bacilos de Gram negativo, *Streptococcus agalactiae* ou *Listeria spp* (14 - 21 dias)				
Abcesso cerebral (4 - 8 semanas)				
Osteomielite hematogénea (4 - 8 semanas)				
Artrite séptica (2- 4 semanas)				
Artrite séptica em prótese (2 -3 meses)				
Fasceíte necrotizante/gangrena gasosa (duração variável fundamentada no processo clínico do utente)				
Pericardite bacteriana (4 semanas)				
Endocardite não complicada de válvula nativa (4 semanas)				
Endocardite não complicada de válvula nativa (quando causada por *Streptococcus do grupo viridans* ou *S. bovis* com elevada sensibilidade à penicilina e sensíveis à gentamicina, a duração do tratamento com a associação dos dois fármacos é de duas semanas				
Pós-operatório de endocardite (2 semanas)				
Mediastinitie (10-14 dias)				
Febre tifoide (14 dias)				
Brucelose (≥6 semanas)				
Doença de Lyme (14 - 28 dias)				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		
3 : Responsabilidades do Grupo de Coordenação Local e do Responsável Local do PPCIRA				
CRITÉRIOS	**SIM**	**NÃO**	**N/A**	**EVIDÊNCIA/FONTE**
Existe evidência de que um médico do grupo de coordenação local do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos, através da implementação de programa de apoio à prescrição antibiótica, assegura a suspensão da terapêutica antibiótica sempre que não houver confirmação de existência de infeção bacteriana				
Existe evidência de que um médico do grupo de coordenação local do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos, através da implementação de programa de apoio à prescrição antibiótica, assegura a limitação da duração da terapêutica antibiótica de acordo com o indicado na presente Norma				
Sub-Total	**0**	**0**	**0**	
ÍNDICE CONFORMIDADE		0%		

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Avaliação de cada padrão: $x = \frac{Total\ de\ respostas\ SIM}{Total\ de\ respostas\ aplicáveis}$ x 100= (IQ) de .....%

7. A presente Norma, atualizada com os contributos científicos recebidos durante a discussão pública, revoga a versão de 8/05/2014 e será atualizada sempre que a evolução da evidência científica assim o determine.
8. A presente Norma é complementada com o seguinte texto de apoio que orienta e fundamenta a sua implementação.

Francisco George
Diretor-Geral da Saúde

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TEXTO DE APOIO

Conceito, definições e orientações

A. Foram utilizados os Graus de Recomendação e os Níveis de Evidência adotados pela Direção-Geral da Saúde, para a emissão de Normas de Orientação Clínica.

B. Esta norma aplica-se à população de utentes, crianças, jovens e adultos com infeções bacterianas, referindo-se as especificidades relativas à população pediátrica.

C. A duração da terapêutica antibiótica para a resolução do quadro clínico depende do estado imunitário do doente, pelo que estas recomendações se destinam apenas a doentes imunocompetentes. Para efeito desta norma, consideram-se imunocompetentes os doentes que não estejam neutropénicos (<500PMN/mm3), não estejam sob tratamento imunossupressor (quimioterapia, radioterapia ou corticoterapia de longa duração ou em doses equivalentes superiores ou iguais a 20 mg/dia de prednisolona ou a 2 mg/Kg/dia se peso inferior a 20kg, nos últimos três meses), que não tenham imunodeficiência primária e que não tenham doença que reduza significativamente a resistência à infeção (leucemia, linfoma, SIDA).

D. Na infeção urinária, a utilização de um esquema de terapêutica antibiótica com duração não superior a 7 dias é também eficaz na presença de cateter urinário. No entanto, se houver resolução lenta da sintomatologia ou bacteriemia poderá ser necessário o prolongamento da mesma (10 dias). A substituição da algália (ou mesmo a sua retirada) após o início da terapêutica antibiótica (para remoção dos biofilmes) poderá facilitar a resolução clínica.

E. A bacteriúria assintomática apenas deve ser tratada na mulher grávida e nos doentes que vão ser submetidos a procedimentos urológicos e com 1 a 7 dias de antibióticos (ver norma 015/2011 da Direção Geral da Saúde).

F. Designa-se por complicada, a infeção urinária associada à presença de anomalias estruturais das vias urinárias, litíase, bexiga neurogénica, algaliação permanente, diabetes mellitus ou gravidez.

G. A duração da terapêutica antibiótica na pneumonia é empírica. Habitualmente é recomendado um mínimo de 5 dias, dependendo dos fármacos usados e da velocidade de resolução dos sintomas, devendo manter-se a terapêutica antibiótica pelo menos 48h depois da resolução destes.

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H. A duração da terapêutica antibiótica nas complicações supurativas de infeção pulmonar depende da eficácia da drenagem (percutânea ou cirúrgica) e na velocidade de resolução clínica. A maioria dos abcessos pulmonares resolve apenas com terapêutica médica prolongada.

I. A duração da terapêutica antibiótica em infeções intra-abdominais está profundamente relacionada com a eficácia do controlo do foco infecioso, o qual deve ser sempre que possível realizado. Na presença de controlo adequado do foco, são suficientes 4 a 7 dias de terapêutica antibiótica.

J. Nas perfurações gástricas e jejunais proximais, na ausência de malignidade ou terapêutica com antiácidos, é adequado tratar apenas durante 24 horas, desde que o controlo do foco seja alcançado nas primeiras 24 horas.

K. As lesões traumáticas ou iatrogénicas do intestino reparadas nas primeiras 12 horas e sem evidência de contaminação peritoneal por conteúdo entérico podem igualmente ser tratadas com antimicrobianos ≤ 24 horas, uma vez que a proliferação bacteriana é mínima.

L. A amigdalite bacteriana tem como tratamento recomendado um administração única de penicilina benzatínica; em alternativa poderá, se necessário, ser usada terapêutica com dez dias de amoxicilina.

M. Lenta resolução clínica na presença de infeção de pele e tecidos moles, otite, amigdalite ou rinosinusite pode estar associada à presença de abcesso, implicando, nesse caso, identificação e controlo do foco.

N. A duração da terapêutica antibiótica nos doentes com bacteriemia depende do foco primário de infeção, do agente envolvido, da possibilidade de controlo do foco e da velocidade de resposta.

O. A terapêutica antibiótica deve ser prolongada em situações em que haja ou se presuma haver:

1) Incapacidade de promover concentrações eficazes do antibiótico no tecido infetado:

   a) Baixa taxa de atividade metabólica do organismo infetante;

   b) Sensibilidade diminuída do organismo infetante ao antibiótico usado;

   c) Presença de biofilmes que não possam ser removidos (associados a material exógeno);

   d) Presença de organismos com alta virulência e capacidade reconhecida de fazer infeções metastáticas;

   e) Em qualquer das situações referidas é fortemente recomendado que seja obtido o controlo; do foco infecioso (em particular remoção de material exógeno infetado, desbridamento de tecidos necrosados e drenagem de abcessos).

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P. A penetração e difusão de múltiplos antibióticos no tecido osteoarticular são deficientes, pelo que concentrações eficazes são atingidas mais lentamente. O próprio metabolismo bacteriano a esse nível (dada a escassez de nutrientes disponíveis) é lento, o que contribui para diminuir a suscetibilidade aos antibacterianos. Nestas condições o controlo do foco é prioritário para a resolução da infeção.

Q. Na infeção articular associada a prótese, a duração da terapêutica antibiótica deve ser prolongada, pelo menos por 2 a 3 meses e a colocação de nova prótese deve ser protelada em pelo menos 6 semanas, após o fim da terapêutica antibiótica. A abordagem conservadora ou a substituição imediata da prótese só devem ser realizadas em condições excecionais.

R. A endocardite de válvula nativa não complicada (abcesso peri-valvular, foco metastático) deve ser tratada durante 4 semanas. Este período deve ser alargado para 6 semanas na presença de alguma dessas complicações, de infeção por *Enterococcus spp* ou na presença de prótese valvular. Em casos selecionados de infeção de válvula nativa não complicada causada por *Streptococcus spp* sensível à penicilina ou por *Staphylococcus* sensível à meticilina, se houver boa resposta clínica com negativação precoce das hemoculturas, a duração da terapêutica pode ser reduzida para 2 semanas (eventualmente em combinação com um aminoglicosídeo).

Na presença de bactérias resistentes, a terapêutica poderá ser prolongada para 8 semanas. Em doentes que tenham sido submetidos a cirurgia, a terapêutica antibiótica deverá ser prolongada duas semanas após a intervenção com terapêutica antibiótica dirigida. Se o exame microbiológico da válvula mostrar persistência dos microrganismos, é proposto um período de 4 semanas, embora um estudo tenha demonstrado igual eficácia com 2 semanas.

S. Embora a avaliação clínica adequada deva constituir a base da decisão quanto á duração da antibioterapia, a utilização da evolução de biomarcadores, como a proteína C reativa e a procalcitonina pode ajudar a individualizar esta decisão.

Fundamentação

A. Os antibióticos são moléculas químicas que interferem com funções vitais das células dos microrganismos, promovendo a sua morte ou a inibição do seu crescimento. *In vitro,* a velocidade de morte desses organismos pode ser extremamente rápida quando expostos a concentrações eficazes de antibióticos. No entanto, a organização dos microrganismos no tecido infetado e a dificuldade na

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difusão dos antibióticos podem dificultar e atrasar a sua atividade, nomeadamente quando há formação de abcessos ou biofilmes, necrose dos tecidos ou condicionantes ambientais que interferem com a atividade metabólica dos microrganismos, determinando diminuição da atividade de alguns antibióticos.

B. A terapêutica antibiótica interfere com o microbioma do indivíduo, rompendo equilíbrios ecológicos delicados. Pode assim facilitar a proliferação de organismos mais virulentos, que se encontram habitualmente inibidos por interação competitiva. Por outro lado, promove a desrepressão e disseminação de genes responsáveis pela resistência aos antimicrobianos (inclusive resistência cruzada) e confere vantagem adaptativa a espécies menos suscetíveis.
C. Está demonstrado *in vivo* que o prolongamento do tempo de terapêutica antibiótica promove a diminuição progressiva da suscetibilidade dos organismos aos antibióticos e promove a proliferação de espécies virulentas naturalmente resistentes. Alguns estudos levantam igualmente a possibilidade de que a exposição prolongada aos antibióticos aumente não só a resistência dos microrganismos mas igualmente o número total de infeções e, em última análise, a mortalidade. Assim, o prolongamento da terapêutica antibiótica para além dos 7 dias deve ser limitado a situações clínicas bem identificadas em que seja reconhecida essa necessidade.
D. Nos últimos anos foi demonstrado em diversos estudos e estabeleceu-se um consenso que a duração da terapêutica antibiótica em infeções não complicadas deve ser reduzida a não mais de 7 dias, devendo ser promovidas doses de antibiótico que facilitem a sua ação bactericida e evitadas exposições prolongadas, assim reduzindo a emergência de microrganismos resistentes e a ocorrência de infeções subsequentes.
E. A duração da terapêutica antibiótica na pielonefrite é condicionada pela velocidade de resolução clínica e pela eficácia bactericida do antibiótico selecionado. Numa metanálise, a terapêutica antibiótica de curta duração (7 dias) demonstrou eficácia igual à terapêutica antibiótica mais prolongada, incluindo nos doentes com bacteriemia. A escolha de antibióticos com concentração elevada no rim e na urina pode ajudar a resolver a infeção e a reduzir a duração da terapêutica antibiótica.
F. Vários estudos e uma metanálise confirmaram que 7 dias de terapêutica antibiótica para pneumonia da comunidade não necrotizante eram seguros e apresentavam uma eficácia pelo menos igual a uma duração de terapêutica antibiótica maior.

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G. Também na pneumonia adquirida em meio hospitalar foi demonstrado que 7 dias de terapêutica antibiótica têm eficácia similar a períodos mais prolongados (10-15 dias). Paralelamente, o número de infeções subsequentes por organismos multirresistentes foi menor no grupo de doentes submetidos a períodos mais curtos de terapêutica antibiótica. Salienta-se, no entanto, maior número de recidivas nos doentes infetados com bacilos de Gram negativo não fermentadores, mas sem que houvesse diferença de mortalidade.

H. Em doentes com pneumonia e com culturas microbiológicas fidedignas negativas, a descontinuação da terapêutica antibiótica não resultou em aumento da mortalidade.

I. Na infeção intra-abdominal, em doentes críticos ou em que o controlo do foco é inadequado, a duração ideal da terapêutica antibiótica é incerta, dependendo da evolução clínica, laboratorial e imagiológica do doente.

J. Relativamente a bacteriemia, numa metanálise em que foram excluídos os doentes com endocardite, não foi encontrada diferença entre a utilização de períodos curtos de terapêutica antibiótica (5-7 dias) e períodos prolongados (>7 dias), independentemente do foco de infeção. Também os estudos que avaliaram a duração da terapêutica de diferentes focos de infeção não encontraram benefício do prolongamento da mesma em função da presença de bacteriemia.

K. Classicamente considera-se que a presença de resposta lenta à terapêutica antibiótica, de foco persistente de infeção não drenável ou de imunossupressão são razões para prolongar a terapêutica antibiótica.

L. Na bacteriemia associada a cateter venoso central, na presença de foco facilmente removível, quando há resolução clínica completa apenas com o controlo do foco, parece não haver necessidade de terapêutica antibiótica, nomeadamente para tratamento de bactérias de Gram negativo ou *Staphylococcus* coagulase negativo, pelo que esta deverá ser limitada a não mais de 3 dias. Já o isolamento de *Staphylococcus aureus*, mesmo em doentes assintomáticos e após exclusão de endocardite e de focos metastáticos, implica um tratamento de pelo menos 14 dias (tempo total de terapêutica antibiótica), dado o risco de recidiva.

M. O tratamento antibiótico da meningite é condicionado pela velocidade de multiplicação dos agentes infeciosos, pelo risco associado à recidiva, pela difusão dos antibacterianos através da barreira hematoencefálica e pelo risco de criação de "santuários".

N. A presença de controlo inadequado do foco, nomeadamente múltiplas coleções abcedadas, que impossibilitem a drenagem cirúrgica ou percutânea (em particular na região abdominal), persistência

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de material exógeno que não possa ser retirado (risco cirúrgico muito elevado), tecido necrosado não desbridável (em particular osso), tromboflebite supurativa (4-6 semanas de terapêutica antibiótica) obriga ao prolongamento do tempo de terapêutica antibiótica, o qual deve ser guiado pela evolução do doente, dos aspetos imagiológicos e dos biomarcadores. Esta estratégia tem eficácia limitada, devendo ser promovido o controlo do foco, sempre que possível.

O. Múltiplos estudos têm demonstrado que medidas integradas de gestão da política de antibióticos, nomeadamente programas de apoio à prescrição antibiótica (*antimicrobial stewardship programs*) estão associadas a diminuição da prevalência de bactérias multirresistentes e à diminuição do consumo de antimicrobianos.

Avaliação

A. A avaliação da implementação da presente Norma é contínua, executada a nível local, regional e nacional, através de processos de auditoria interna e externa.

B. A parametrização dos sistemas de informação para a monitorização e avaliação da implementação e impacte da presente Norma é da responsabilidade das administrações regionais de saúde e das direções dos hospitais.

C. A efetividade da implementação da presente Norma nos cuidados de saúde primários e nos cuidados hospitalares e a emissão de diretivas e instruções para o seu cumprimento é da responsabilidade dos conselhos clínicos dos agrupamentos de centros de saúde e das direções clínicas dos hospitais.

D. A implementação da presente Norma é monitorizada e avaliada através dos seguintes indicadores:

1) Taxa de cursos de terapêutica antibiótica com duração não superior a 7 dias:

   a) Numerador: número de cursos de terapêutica antibiótica não superior a 7 dias;

   b) Denominador: número de cursos de terapêutica antibiótica.

2) Taxa de adesão á justificação da necessidade de terapêutica antibiótica com duração superior a 7 dias:

   a) Numerador: número de cursos de terapêutica antibiótica superior a 7 dias com explanação da justificação no processo clínico;

   b) Denominador: número de cursos de terapêutica antibiótica superior a 7 dias.

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3) Taxa de cursos de terapêutica antibiótica com duração superior a 7 dias concordantes com a Norma:

   a) Numerador: número de cursos de terapêutica antibiótica superior a 7 dias com critério adequado (de acordo com a Norma);

   b) Denominador: número de cursos de terapêutica antibiótica superior a 7 dias.

Comité Científico

A. A presente Norma foi elaborada no âmbito do Departamento da Qualidade na Saúde da Direção-Geral da Saúde, do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos e do Conselho para Auditoria e Qualidade da Ordem dos Médicos, através dos seus colégios de especialidade, ao abrigo do protocolo existente entre a Direção-Geral da Saúde e a Ordem dos Médicos.

B. A proposta da presente Norma foi elaborada por João Gonçalves Pereira, José Artur Paiva e António Sousa Uva (coordenação científica).

C. A elaboração da proposta da presente Norma teve ainda o apoio da Comissão Cientifica do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos.

D. Todos os peritos envolvidos na elaboração da presente Norma cumpriram o determinado pelo Decreto-Lei n.º 14/2014 de 22 de janeiro, no que se refere à declaração de inexistência de incompatibilidades.

E. A avaliação científica do conteúdo final da presente Norma foi efetuada no âmbito do Departamento da Qualidade na Saúde.

Coordenação Executiva

Na elaboração da presente Norma a coordenação executiva foi assegurada por Cristina Martins d'Arrábida, do Departamento da Qualidade na Saúde da Direção-Geral da Saúde.

Comissão Científica para as Boas Práticas Clínicas

Pelo Despacho n.º 7584/2012, do Secretário de Estado Adjunto do Ministro da Saúde, de 23 de maio, publicado no Diário da República, 2.ª série, n.º 107, de 1 de junho de 2012, a Comissão Científica para as

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Boas Práticas Clínicas tem como missão a validação científica do conteúdo das Normas Clínicas emitidas pela Direção-Geral da Saúde. Nesta Comissão, a representação do Departamento da Qualidade na Saúde é assegurada por Henrique Luz Rodrigues.

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NORMA

NÚMERO:	004/2020
DATA:	23/03/2020
ATUALIZAÇÃO:	14/10/2020

Maria da Graça Gregório de Freitas

Digitally signed by Maria da Graça Gregório de Freitas
DN: c=PT, o=Direção-Geral da Saúde, cn=Maria da Graça Gregório de Freitas
Date: 2020.10.29 16:47:22 Z

ASSUNTO:	**COVID-19: Abordagem do Doente com Suspeita ou Confirmação de COVID-19**
PALAVRAS-CHAVE:	COVID-19, SARS-CoV-2, SNS24, Áreas Dedicadas
PARA:	Sistema de Saúde
CONTACTOS:	normas@dgs.min-saude.pt

Desde o reconhecimento da doença pelo novo coronavírus (COVID-19) como Pandemia pela Organização Mundial de Saúde que têm sido adotadas várias medidas para prevenir e conter a transmissão do vírus SARS-CoV-2. Estas medidas incluíram a implementação, pela Norma 004/2020 da Direção-Geral da Saúde (DGS), de um modelo inovador de abordagem dos doentes com suspeita e confirmação de infeção por SARS-CoV-2 no Serviço Nacional de Saúde (SNS), assente numa resposta adequada, atempada e articulada de todo o sistema de saúde.

A rápida evolução científica impõe uma atualização permanente da abordagem clínica das pessoas com suspeita e infeção confirmada por SARS-CoV-2, que se pretende mais sustentada em evidência e continuamente adaptada à evolução epidemiológica e às medidas de Saúde Pública implementadas. Em Portugal, a evolução epidemiológica da COVID-19 revelou-se heterogénea, o que justifica um modelo de gestão clínica capaz de se adaptar às circunstâncias a nível regional e local, e de integrar a experiência entretanto acumulada, num ciclo de melhoria contínua da qualidade.

Considerando os desafios da época de outono-inverno, o crescimento epidémico da COVID-19 e o inevitável aumento da incidência de outras infeções respiratórias agudas clinicamente indistinguíveis da infeção por SARS-CoV-2, nomeadamente, a gripe, importa evoluir na abordagem e acompanhamento clínico dos doentes com suspeita e confirmação de COVID-19.

Em concreto, importa definir um modelo assente no cumprimento das medidas de prevenção e controlo de infeção, no diagnóstico diferencial rápido das infeções respiratórias agudas, com base na utilização adequada e precoce de testes laboratoriais, na separação de circuitos, e na melhoria da eficiência, qualidade e segurança do seguimento clínico dos doentes com suspeita ou infeção por SARS-CoV-2.

Assim, nos termos da alínea a) do nº 2 do artigo 2º do Decreto Regulamentar nº 14/2012, de 26 de janeiro, a Direção-Geral da Saúde procede à atualização da Norma n.º 004/2020:

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1. O modelo de abordagem de casos suspeitos e confirmados de infeção por SARS-CoV-2 (COVID-19) é implementado através das medidas e ações das várias entidades do Ministério da Saúde, nos termos do Anexo 1 da presente Norma.

2. A reorganização das unidades hospitalares estabelecida pela presente Norma não se aplica, entre outras defendidas pelas Administrações Regionais de Saúde (ARS) ao Instituto Português de Oncologia cujas unidades em Coimbra, Lisboa e Porto constituem unidades hospitalares *COVID-19-free,* devendo garantir o encaminhamento dos casos suspeitos para as unidades prestadoras de cuidados de saúde apropriadas.

3. A abordagem clínica de doentes com suspeita ou com infeção confirmada por SARS-CoV-2 que constituam grupos específicos ou de maior vulnerabilidade, entre os quais **grávidas**, **recém-nascidos**, pessoas com **doença renal crónica em programa de diálise** e pessoas com **doença oncológica**, e **residentes em ERPI ou estruturas similares**, deve seguir as orientações específicas da DGS para estes grupos.

4. As **pessoas com um resultado positivo num teste laboratorial para SARS-CoV-2 sem qualquer manifestação clínica** de doença à data do diagnóstico laboratorial são considerados **doentes com COVID-19 assintomática e têm indicação para vigilância clínica e isolamento no domicílio**, nos termos da presente Norma.

5. É revogada a Norma n.º 010/2020 da DGS.

Abordagem da Suspeita de Infeção por SARS-CoV-2

6. As pessoas que desenvolvam os sintomas abaixo indicados são consideradas **suspeitas de infeção por SARS-CoV-2 (COVID-19)**:
    a. Quadro clínico sugestivo de **infeção respiratória aguda** com pelo menos um dos seguintes sintomas[1–3]:
        i. Tosse de novo, ou agravamento do padrão habitual, ou associada a cefaleias ou mialgias, ou;
        ii. Febre (temperatura ≥ 38.0ºC) sem outra causa atribuível, ou;
        iii. Dispneia / dificuldade respiratória, sem outra causa atribuível.
    b. Anosmia, ageusia ou disgeusia de início súbito.

7. Os doentes com suspeita de infeção por SARS-CoV-2 (COVID-19) contactam a Linha SNS24 (808 242424) ou, de forma complementar, outras linhas telefónicas criadas especificamente para o efeito, pelas Administrações Regionais de Saúde (ARS), em articulação com os Agrupamentos de Centros de Saúde (ACES), em Unidades de Saúde Familiar (USF) ou Unidades de Cuidados de Saúde Personalizados (UCSP), divulgadas a nível regional e local.

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8. A avaliação pelo SNS24, ou pelas linhas telefónicas criadas para o efeito nas USF / UCSP, permite o encaminhamento dos doentes com suspeita de COVID-19 para (Diagrama):
    a. **Vigilância clínica e isolamento no domicílio**;
    b. **Avaliação clínica em Áreas Dedicadas** a Doentes com Suspeita de Infeção Respiratória Aguda (ADR) nos Cuidados de Saúde Primários (ADR-Comunidade, **ADR-C**);
    c. **Avaliação clínica em Áreas Dedicadas** a Doentes com Suspeita de Infeção Respiratória Aguda nos Serviços de Urgência dos Hospitais (**ADR-SU**);
    d. Intervenção da Emergência Médica Pré-Hospitalar, através do Centro de Orientação de Doentes Urgente (CODU) do **INEM**.

9. Todos os doentes com suspeita de infeção por SARS-CoV-2, nos termos do ponto 6 da presente Norma, são notificados na plataforma SINAVE*med*.

10. Todos os doentes com suspeita de infeção por SARS-CoV-2 são submetidos a **teste laboratorial para SARS-CoV-2**, em amostras do trato respiratório (superior e/ou inferior), nos termos da Orientação n.º 015/2020 da DGS[i] e da Circular Informativa DGS/INFARMED/INSA n.º 003/CD/100.20.200[ii].

11. Para efeito do número anterior, o **teste laboratorial para SARS-CoV-2 é requisitado**:
    a. Pelo médico das equipas das USF / UCSP para os doentes com indicação para vigilância clínica e isolamento no domicílio, de forma remota através da plataforma Exames Sem Papel (Anexo 4)[iii];
    b. Pelo médico das equipas das ADR-C ou ADR-SU, ou por qualquer médico que durante a avaliação clínica considere a suspeita de COVID-19;

12. Os resultados dos testes laboratoriais realizados nos termos do ponto 10 da presente Norma são disponibilizados ao doente e registados na plataforma SINAVE*lab* e no Registo de Saúde Eletrónico (RSE) pelo laboratório, no **prazo máximo de 12 horas após a sua realização**, com indicação do n.º de utente SNS (ou na ausência deste, nome completo e data de nascimento) e dos dados geográficos relativos à morada onde o utente reside e cumpre isolamento, **e de forma a não serem ultrapassadas 24 horas desde a requisição do teste laboratorial e a obtenção do seu resultado**.

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[i] Consultar Orientação n.º 015/2020 em https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0152020-de-23032020.aspx.

[ii] Consultar Circular Informativa Conjunta DGS/INFARMED/INSA n.º 003/CD/100.20.200 de 27/05/2020 em https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/circular-informativa-conjunta-dgsinfarmedinsa-n-003cd10020200-de-27052020-.aspx.

[iii] **Os testes laboratoriais para SARS-CoV-2 para os doentes com indicação para vigilância clínica e isolamento no domicílio são requisitados pelo SNS24 na Fase 2 da resposta definida no Plano da Saúde para o Outono-Inverno 2020/2021.**

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13. A investigação epidemiológica é iniciada a todos os doentes com infeção confirmada por SARS-CoV-2, nas primeiras 24 horas após o resultado do teste laboratorial ser registado na plataforma SINAVE*lab*, para rastreio de contactos, nos termos da Norma n.º 015/2020 da DGS[i].

14. Aos doentes com infeção confirmada por SARS-CoV-2 que têm a aplicação STAYAWAY COVID[ii] instalada deve ser gerado o código de legitimação na plataforma *Trace COVID-19* (https://tracecovid19.min-saude.pt/) para o rastreio de contactos, nos termos da Norma n.º 015/2020 da DGS[i].

Vigilância Clínica e Isolamento no Domicílio

15. Têm indicação para permanecer no domicílio, sem necessidade de avaliação clínica inicial presencial em ADR, os doentes que reúnam **todos** os seguintes critérios (Anexo 2):
    a. Idade inferior a 60 anos;
    b. Sintomas ligeiros como febre por período inferior a 3 dias, com boa resposta aos antipiréticos, e/ou tosse;
    c. Ausência de dispneia ou sinais de dificuldade respiratória, hemoptises, vómitos ou diarreia persistentes, ou qualquer outro sintoma de gravidade clínica;
    d. Ausência de doenças crónicas descompensadas ou condições associadas a risco de evolução para COVID-19 com gravidade.

16. Os doentes com indicação para vigilância clínica e isolamento no domicílio que não disponham de condições de habitabilidade e/ou exequibilidade de isolamento no domicílio (Anexo 2) são encaminhados para estruturas residenciais alternativas, criadas ou selecionadas a nível regional ou local, em articulação intersectorial com o Centro Distrital da Segurança Social, as Entidades da Comissão Municipal de Proteção Civil e outros parceiros municipais.

17. As equipas das USF / UCSP realizam a primeira avaliação telefónica **no prazo máximo de 24 horas após o contacto com o SNS24**, ou com as linhas telefónicas criadas especificamente para o efeito.

[i] Consultar Norma n.º 015/2020 em https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0152020-de-24072020.aspx.
[ii] Decreto-Lei n.º 52/2020 de 11 de agosto.

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18. O **teste laboratorial para SARS-CoV-2** é requisitado pelo médico das equipas das USF / UCSP[i] aos doentes com indicação para vigilância e isolamento no domicílio e é realizado, de forma a evitar deslocações excessivas:
    a. No domicílio, através de equipas selecionadas e qualificadas para o efeito (colheita de amostras biológicas do trato respiratório superior no domicílio);
    b. Nos laboratórios selecionados para o efeito, preferencialmente em sistema de *drive-thru*, sempre com pré-agendamento,
    c. Nos espaços dedicados para a colheita de amostras respiratórias do trato respiratório superior nas ADR-C, sempre com pré-agendamento.

19. Os doentes com indicação para vigilância e isolamento no domicílio são acompanhados pelas equipas das USF/UCSP até ser conhecido o resultado do teste laboratorial para SARS-CoV-2, de acordo com o Anexo 4 da presente Norma.

20. Para efeitos do disposto nos números anteriores:
    a. São garantidas as ações constantes no Anexo 1 da presente Norma;
    b. É utilizada a plataforma *Trace COVID-19*.

21. Após a realização do teste laboratorial para SARS-CoV-2:
    a. Se o resultado for **negativo**, os doentes seguem as recomendações dadas pelas equipas das USF/UCSP, cessando a gestão na plataforma *Trace COVID-19,* mas, caso sejam contactos de casos confirmados, mantêm o seguimento nos termos Norma n.º 015/2020;
    b. Perante um resultado **positivo**, os doentes mantêm-se em vigilância clínica pelas equipas das USF/UCSP, e isolamento no domicílio, nos termos do Anexo 4 da presente Norma, até serem estabelecidos os critérios de alta / fim do isolamento.

22. Aos doentes com infeção confirmada por SARS-CoV-2 (COVID-19) é determinado o confinamento obrigatório pela Autoridade de Saúde territorialmente competente (Determinação de Isolamento) e emitido o Certificado de Incapacidade Temporária para o Trabalho (CIT) pelo médico da USF / UCSP.

Avaliação Clínica nas ADR-Comunidade

23. As ADR-Comunidade (ADR-C) são áreas dedicadas exclusivamente à avaliação clínica de doentes com suspeita de infeção respiratória aguda e colheita de amostras para teste

[i] **Os testes laboratoriais para SARS-CoV-2 para os doentes com indicação para vigilância clínica e isolamento no domicílio são requisitados pelo SNS24 na Fase 2 da resposta definida no Plano da Saúde para o Outono-Inverno 2020/2021.**

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laboratorial para SARS-CoV-2, em contexto de Cuidados de Saúde Primários, que cumprem as condições definidas no Anexo 3 da presente Norma.

24. São encaminhados para ADR-C todos os doentes que:
    a. De acordo com o SNS24, ou as linhas telefónicas criadas para o efeito nas USF / UCSP, tenham indicação para avaliação clínica na ADR-C;
    b. Reúnam os seguintes critérios:
        i. Idade superior a 60 anos, e/ou;
        ii. Comorbilidades que não determinam o internamento hospitalar nem apresentam sintomas de descompensação clínica, e;
        iii. Não apresentam dispneia ou dificuldade respiratória, hemoptises, vómitos e diarreia persistentes, ou qualquer outro sintoma ou sinal de gravidade clínica;
    c. Recorram presencialmente às USF / UCSP com os sintomas descritos no ponto 6 da presente Norma, exceto se existir uma ADR-C nessas USF / UCSP, ou se os doentes apresentarem critérios para encaminhamento direto para vigilância clínica e isolamento no domicílio ou para observação na ADR-SU.

25. O transporte para ADR-C é realizado, preferencialmente, em veículo próprio, não devendo ser utilizados transportes públicos.

26. Nas ADR-C os doentes são submetidos a avaliação clínica e encaminhamento:
    a. Os doentes com **suspeita de infeção por SARS-CoV-2**, nos termos do ponto 6 da presente Norma e **indicação para vigilância e isolamento em domicílio**, são submetidos a **colheita de amostra biológica para teste laboratorial para SARS-CoV-2 na ADR-C**. Excecionalmente, quando a colheita de amostra biológica não puder ser realizada na ADR-C nem no domicílio, o doente é encaminhado para os locais disponíveis para o efeito, em cada região ou local;
    b. Os doentes com critérios de avaliação em Serviço de Urgência e/ou com critérios para internamento (Anexo 2), são referenciados para a ADR-SU em veículo próprio ou em ambulância (ativada pelo médico da ADR-C), de acordo com a avaliação clínica.

27. Para efeitos do disposto nos números anteriores:
    a. São garantidas as ações constantes no Anexo 1 da presente Norma;
    b. Para os doentes suspeitos de infeção por SARS-CoV-2, nos termos do ponto 6 da presente Norma, avaliados presencialmente na ADR-C, e com indicação para vigilância e isolamento em domicílio, as equipas da ADR-C:
        i. Procedem à sua notificação na plataforma SINAVE*med* (área *Médicos*);
        ii. Entregam o folheto anexo à Orientação n.º 010/2020 da DGS;
        iii. Procedem à sua inserção ou alteração na plataforma *Trace COVID-19*.

28. Os doentes com indicação para vigilância clínica e isolamento no domicílio são acompanhados pelas equipas das USF/UCS, nos termos do Anexo 4 da presente Norma.

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Avaliação Clínica nas ADR-Serviço de Urgência

29. As ADR-Serviço de Urgência (ADR-SU) são áreas dedicadas exclusivamente à avaliação clínica de doentes com suspeita de infeção respiratória aguda e colheita de amostras para teste laboratorial para SARS-CoV-2, em contexto de urgência hospitalar, que cumprem as condições definidas no Anexo 3 da presente Norma.

30. São encaminhados para ADR-SU todos os doentes que:
    a. De acordo com o SNS24, com as linhas telefónicas criadas para o efeito nas USF / UCSP, com a avaliação clínica na ADR-C, ou com a avaliação clínica durante o seguimento através da plataforma *Trace COVID-19* tenham indicação para avaliação em urgência hospitalar;
    b. Sejam referenciados através do CODU/INEM;
    c. Recorram presencialmente ao SU e apresentem os sintomas descritos no ponto 6 da presente Norma.

31. Nas ADR-SU os doentes com suspeita de infeção por SARS-CoV-2, nos termos do ponto 6 da presente Norma são submetidos a avaliação clínica e encaminhamento (Anexo 2):
    a. Doentes com indicação para vigilância clínica e isolamento em domicílio, isto é, com indicação para alta do serviço de urgência:
        i. **Colheita de amostra biológica para a teste laboratorial para SARS-CoV-2 na ADR-SU;**
        ii. Notificação na plataforma SINAVE*med* (área *Médicos*), pela equipa da ADR-SU, ou equipa definida para o efeito;
        iii. Entrega do folheto anexo à Orientação n.º 010/2020 da DGS, pela equipa da ADR-SU;
        iv. Inserção ou alteração na plataforma *Trace COVID-19*, pela equipa da ADR-SU.
    b. Doentes com indicação para internamento hospitalar:
        i. **Colheita de amostra biológica para a teste laboratorial para SARS-CoV-2 e vírus Influenza[i] na ADR-SU, e sua realização de acordo com a metodologia mais rápida disponível;**
        ii. Notificação na plataforma SINAVE*med* (área *Médicos*), pela equipa da ADR-SU ou equipa definida para o efeito;
        iii. Avaliação dos critérios para admissão em Unidade de Cuidados Intensivos (UCI) (Anexo 2).

[i] A taxa de coinfecção por SARS-CoV-2 e outros vírus respiratórios, particularmente Influenza, ainda é indeterminada. Assim, um teste diagnóstico positivo para um agente não exclui a necessidade de testar para outros, conforme o contexto epidemiológico e suspeita clínica.

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32. Para efeitos do disposto nos números anteriores são garantidas as ações constantes no Anexo 1 da presente Norma.

33. Os **doentes que não apresentem qualquer critério de internamento** (Anexo 2) e que, cumulativamente, cumpram as condições de habitabilidade e exequibilidade do isolamento no domicílio, ou que possam ser encaminhados para uma alternativa domiciliária (estrutura residencial) definida a nível regional ou local, **têm alta do serviço de urgência e aguardam os resultados dos testes laboratoriais no domicílio ou na estrutura residencial.**

34. Os doentes com indicação para vigilância e isolamento no domicílio são acompanhados pelas equipas das USF/UCSP de acordo com a presente Norma.

35. Os doentes com critérios para internamento hospitalar aguardam os resultados na ADR-SU ou em locais criados / selecionados para o efeito.

36. Os doentes com critérios para admissão em UCI realizam o teste laboratorial **de acordo com a metodologia mais rápida disponível** e são **referenciados o mais precocemente possível** às equipas de Medicina Intensiva, de acordo com os protocolos locais de atuação, e sem aguardar pelo resultado do teste laboratorial.

Internamento Hospitalar

37. O internamento hospitalar é organizado da seguinte forma:
    a. Doentes com **teste laboratorial para SARS-CoV-2 positivo**: enfermarias ou UCI dedicadas a doentes com COVID-19;
    b. Doentes com **teste para SARS-CoV-2 negativo**, **mas com suspeita clínica de COVID-19 ou de infeção respiratória aguda**: áreas intermédias, fisicamente separadas das ADR-SU, ou enfermarias ou UCI dedicadas a doentes com COVID-19, onde devem **realizar novo teste laboratorial para SARS-CoV-2**[7], nos termos da Orientação n.º 015/2020 da DGS[i];
    c. Doentes com **teste para SARS-CoV-2 negativo e sem suspeita clínica de COVID-19 ou de infeção respiratória aguda**: enfermarias ou UCI não-COVID-19.

38. Para o efeito do disposto nos números anteriores:
    a. São garantidas as ações constantes no Anexo 1 da presente Norma.

i Consultar Orientação n.º 015/2020 em https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0152020-de-23032020.aspx.

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b. Os Grupos Coordenadores Locais do Programa de Prevenção e Controlo de Infeções e Resistência a Antimicrobianos (**GCL-PPCIRA**) devem ajustar os circuitos hospitalares de forma a garantir:
    i. Nos serviços de urgência, a efetiva separação dos doentes com suspeita de infeção respiratória aguda face aos restantes;
    ii. No internamento hospitalar (enfermaria e UCI), a efetiva separação dos doentes com COVID-19 face aos restantes através da criação de coortes nos casos de coinfecção por SARS-CoV-2 e por outros vírus respiratórios, particularmente vírus da gripe.

Abordagem Terapêutica dos Doentes com COVID-19 em Regime de Internamento

39. O tratamento recomendado para os doentes internados com COVID-19 é[2,9];
    a. Tratamento sintomático e de suporte, tendo em consideração a situação clinica e as comorbilidades[10];
    b. Implementação de *scores* de vigilância e monitorização clínica[11–14];
    c. Oxigenoterapia para $SatO_2$ > 94% por dispositivos sem humidificação;
    d. Terapêutica broncodilatadora sem aerossolização;
    e. Tromboprofilaxia com heparina de baixo peso molecular, exceto se contraindicada[15,16];
    f. Terapêutica antivírica com Remdesivir de acordo com os critérios da presente Norma e o procedimento, enquadrado no âmbito de um Programa de Acesso Precoce.

40. A terapêutica com **Remdesivir** deve ser administrada o mais precocemente possível, nos **doentes internados que reúnam todos os seguintes critérios**:
    a. Confirmação laboratorial de SARS-CoV-2;
    b. Pneumonia (confirmada em radiograma do tórax ou tomografia computorizada)[2,17,18];
    c. Necessidade de oxigenoterapia suplementar por saturação de O_2 inferior a 94%[i];
    d. Idade igual ou superior a 12 anos[ii];
    e. Peso corporal igual ou superior a 40 Kg;

41. A administração de Remdesivir deve ser feita com precaução em doentes com[iii]:
    a. Hipersensibilidade conhecida aos excipientes;

[i] Aferida por gasimetria arterial, ou equivalente (capilar) nos doentes pediátricos, em ar ambiente.
[ii] A administração de Remdesivir em doentes com COVID-19 grave, com idade inferior a 12 anos e/ou peso corporal entre 3,5 e 40 Kg, não está recomendada, pelo que a sua utilização só pode ser considerada, a título compassivo, ao abrigo do artigo 92.º do Decreto-Lei n.º 176/2006 de 31 de Agosto, desde que o médico assistente considere benefício clínico face ao risco da sua administração[19–22].
[iii] Consultar RCM do fármaco, disponível em https://www.ema.europa.eu/en/documents/product-information/veklury-epar-product-information_pt.pdf

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b. Valores de alanina aminotransferase (ALT) superiores a 5 vezes o limite superior do valor de referência (conforme unidades do laboratório local);
c. Taxa de filtração glomerular estimada inferior a 30 mL/minuto.

42. Para os doentes adultos e pediátricos com idade superior a 12 anos e peso corporal superior a 40 Kg, a administração endovenosa de Remdesivir é realizada de acordo com o seguinte esquema posológico:
    a. Dia 1 de tratamento: 200 mg, EV, durante 30 a 120 minutos;
    b. Dias 2 a 5 de tratamento: 100 mg, EV, a cada 24 horas, durante 30 a 120 minutos.
    c. O tratamento é de 5 dias, com possibilidade de extensão até um máximo de 10 dias, na ausência de melhoria clínica e considerado o risco-benefício.

43. Nos doentes propostos para terapêutica com Remdesivir realiza-se:
    a. Estimativa da taxa de filtração glomerular antes do início da terapêutica;
    b. Avaliação das aminotransferases antes do início e diariamente, durante a terapêutica;
    c. Implementação de plano de farmacovigilância que garanta uma monitorização rigorosa e reporte atempado de reações adversas medicamentosas.

44. A administração de Remdesivir deve ser descontinuada em doentes que desenvolvam:
    a. Valores de ALT superiores a 5 vezes o limite superior do valor de referência (conforme unidades do laboratório local), podendo ser reiniciado quando o valor de ALT for inferior a 5 vezes o limite superior do valor de referência;
    b. Elevação da ALT acompanhada por sinais ou sintomas de lesão hepática, aumento da bilirrubina conjugada, da fosfatase alcalina ou da relação normalizada internacional (INR)[22].

45. A administração de **Dexametasona**[i] nos doentes com infeção por SARS-CoV-2[9,23–28]:
    a. **Deve ser considerada** nos doentes adultos e pessoas, a partir dos 12 anos de idade e com peso superior ou igual a 40 kg, internados em fase de doença grave e crítica (Anexo 2), a partir do 7.º dia após o início dos sintomas, desde que assegurado o benefício face ao risco da sua administração.
    b. **Não está recomendada** nos doentes com doença ligeira a moderada, particularmente em estádios precoces da doença (até ao 7º dia após o início dos sintomas), exceto se existir indicação por comorbilidades pré-existentes.
46. A dose recomendada de Dexametasona em adultos e pessoas a partir dos 12 anos de idade é de 6 mg, uma vez por dia, até 10 dias[28], podendo ser administrada por via entérica ou administrada por injeção ou perfusão.

[i] A utilização de outros corticoides, nomeadamente a Metilprednisolona, pode ser considerada, sobretudo em idade pediátrica.

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47. Nos doentes com COVID-19 grave em fase de recuperação, particularmente naqueles com internamento prolongado ou em UCI, deve ser garantido um plano de reabilitação respiratória, neuromuscular e osteoarticular[29–32].

Critérios de Alta Hospitalar e de Hospitalização Domiciliária

48. Os doentes adultos internados com COVID-19 podem ser transferidos para **Unidades de Hospitalização Domiciliária** (Norma n.º 20/2018 da DGS[i]) se cumulativamente reunirem os seguintes critérios:
    a. Permanência em internamento, pelo menos, até ao 8.º dia de sintomas;
    b. Critérios de habitabilidade e exequibilidade do isolamento no domicílio, constantes no Anexo 2 da presente Norma.

49. Os doentes internados com COVID-19 podem ter **alta hospitalar** e manter a vigilância clínica e o isolamento no domicílio quando, de acordo com a avaliação clínica, apresentam cumulativamente:
    a. Evolução clínica favorável;
    b. Apirexia mantida há pelo menos 3 dias, sem utilização de antipiréticos;
    c. Ausência de insuficiência respiratória ou necessidade de oxigenoterapia;
    d. Ausência de agravamento imagiológico;
    e. Cumprimento dos critérios de habitabilidade exequibilidade do isolamento no domicílio, constantes no Anexo, ou possibilidade de encaminhamento para uma alternativa domiciliária definida a nível regional ou local.

50. Para o efeito do disposto nos números anteriores, as equipas hospitalares:
    a. Entregam o folheto anexo à Orientação n.º 010/2020 da DGS;
    b. Procedem à sua inserção ou alteração na plataforma Trace COVID-19.

Critérios de Alta Clínica e Fim das Medidas de Isolamento

51. O fim das medidas de isolamento dos **doentes sintomáticos** com COVID-19 é determinado pelo cumprimento dos seguintes critérios, **sem necessidade de realização de teste laboratorial para SARS-CoV-2**, e de acordo com a gravidade clínica (Anexo 2)[33–36]:

    a. **Doença ligeira ou moderada**: **10 dias** desde o início dos sintomas, desde que:
        i. Apirexia (sem utilização de antipiréticos) durante **3 dias** consecutivos, **e;**

[i] Consultar Norma n.º 20/2018 em https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0202018-de-20122018-pdf.aspx

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ii. Melhoria significativa dos sintomas durante **3 dias** consecutivos[i];

b. **Doença grave ou crítica: 20 dias** desde o início dos sintomas, desde que:
   i. Apirexia (sem utilização de antipiréticos) durante **3 dias** consecutivos, **e;**
   ii. Melhoria significativa dos sintomas durante **3 dias** consecutivos[ii];

c. Situações de **imunodepressão grave**, independentemente da gravidade da doença, (Anexo 2): **20 dias** desde o início dos sintomas, desde que:
   i. Apirexia (sem utilização de antipiréticos) durante **3 dias** consecutivos, **e;**
   ii. Melhoria significativa dos sintomas durante **3 dias** consecutivos[iii];

52. **Para os doentes com COVID-19 assintomática**, isto é, pessoas sem qualquer manifestação clínica de doença à data do diagnóstico laboratorial e até ao final do seguimento clínico, **o fim das medidas de isolamento é determinado 10 dias** após a realização do teste laboratorial que estabeleceu o diagnóstico de COVID-19.

53. **Para as situações seguintes, o fim das medidas de isolamento é determinado pelo cumprimento dos critérios definidos nos pontos anteriores, acrescido da obtenção de um teste laboratorial para SARS-CoV-2 negativo**, realizado no momento em que os critérios definidos no ponto anterior são estabelecido[37–39]:
   a. Profissionais de saúde ou prestadores de cuidados de elevada proximidade[iv] a pessoas vulneráveis (Anexo 2), incluindo profissionais das ERPI, que iniciam atividade laboral após o fim do isolamento;
   b. Doentes que vão ser admitidos em ERPI, unidades da RNCC, unidades de cuidados paliativos, ou similares;
   c. Necessidade de transferência intra-hospitalar para áreas não-dedicadas a doentes COVID-19.
54. Quando, nas situações indicadas no ponto anterior, o resultado do teste laboratorial para SARS-CoV-2 for positivo, o isolamento é prolongado até completar 20 dias desde o início dos sintomas, determinando-se, nessa altura, o fim do isolamento, **sem necessidade de realização adicional de teste laboratorial**[6,36].

55. **Nos 90 dias após o diagnóstico laboratorial de infeção por SARS-CoV-2 não deve ser realizado novo teste laboratorial para diagnóstico de SARS-CoV-2[4–6] exceto nas pessoas que desenvolvam os sintomas** descritos no ponto 6 da presente Norma **e que:**

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i Excetuando anosmia, ageusia e disgeusia, que podem persistir durante semanas, não devendo ser avaliados na decisão de término de isolamento.
ii Excetuando anosmia, ageusia e disgeusia, que podem persistir durante semanas, não devendo ser avaliados na decisão de término de isolamento.
iii Excetuando anosmia, ageusia e disgeusia, que podem persistir durante semanas, não devendo ser avaliados na decisão de término de isolamento.
iv Entende-se por cuidados de elevada proximidade, a prestação de procedimentos como higiene pessoal, alimentação e cuidados que impliquem um contacto físico direto a uma distância inferior a 2 metros e durante 15 minutos ou mais.

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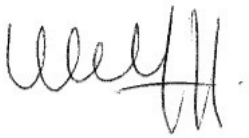
a. Simultaneamente:
    i. Sejam contato de alto risco de um caso confirmado de COVID-19, nos últimos 14 dias;
    ii. Não exista diagnóstico alternativo (incluindo outros vírus respiratórios) para o quadro clínico.
b. Apresentem situações clínicas de imunodepressão (Anexo 2).

56. Para os doentes com suspeita ou confirmação de COVID-19 nos quais se verifique o **óbito** são aplicados os procedimentos descritos na Norma n.º 002/2020 da DGS[i].

57. Deve constar no processo clínico a decisão fundamentada da eventual impossibilidade da aplicação da presente Norma.

58. O conteúdo da presente Norma será atualizado sempre que a evidência científica assim o justifique.



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i Consultar Norma n.º 002/2020 em: https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0022020-de-16032020.aspx

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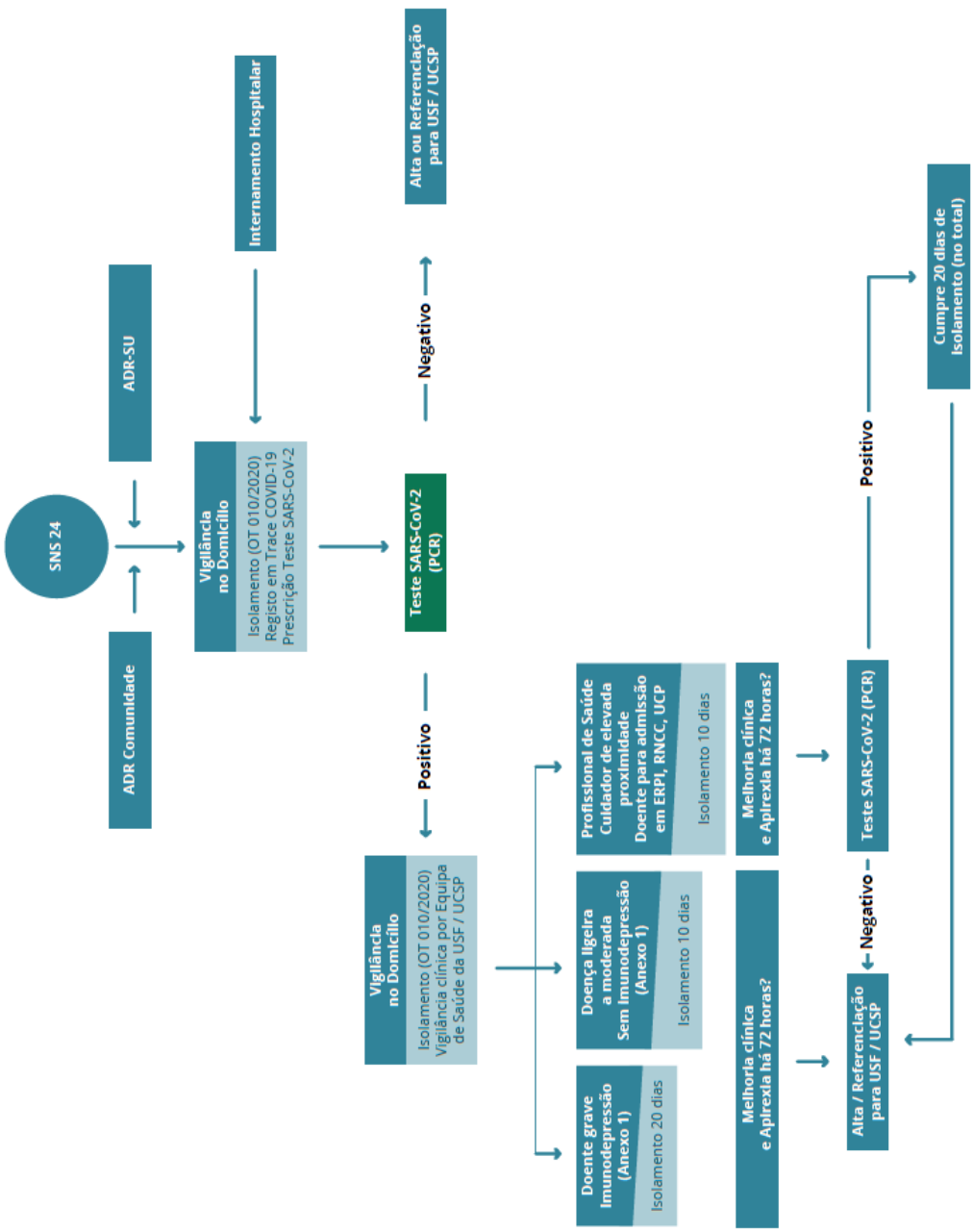
FLUXOGRAMAS

Vigilância Clínica e Isolamento no Domicílio



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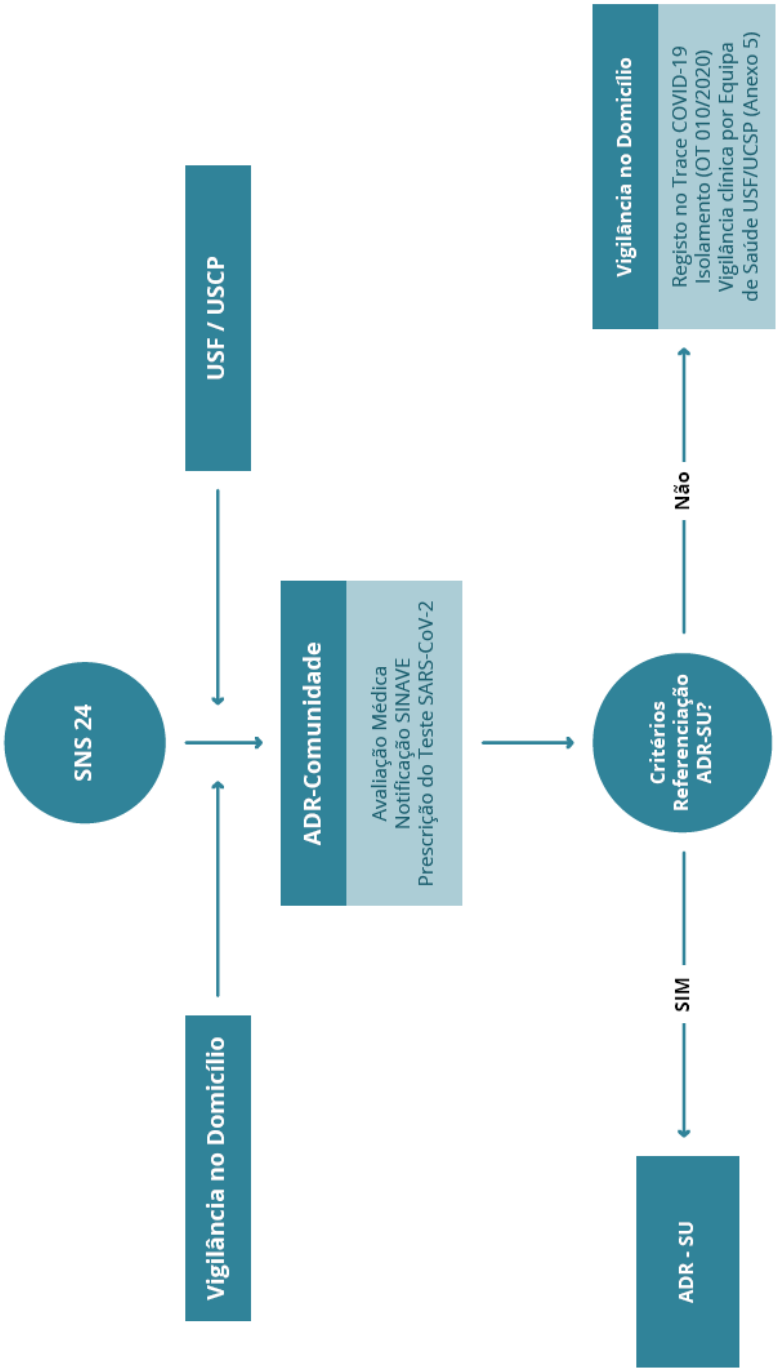
Avaliação Clínica na ADR – C



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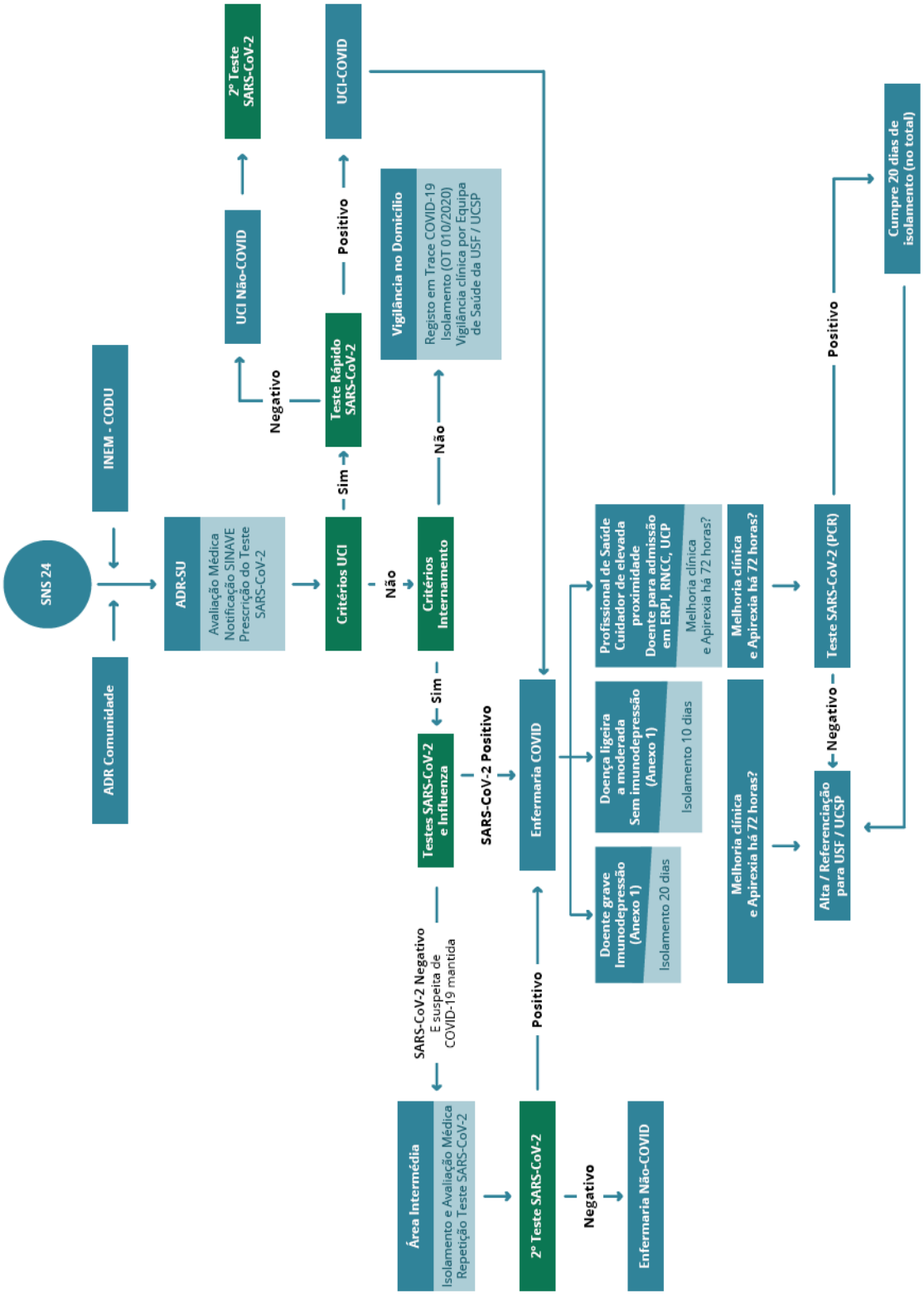
Avaliação Clínica na ADR – SU e Internamento Hospitalar



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ANEXO 1

Atividades a desenvolver pelas entidades competentes pela operacionalização da presente Norma

Entidade(s)	Medidas e Ações
Centro de Contacto **SNS24**, e **SPMS**, EPE.	1. Encaminhamento clínico e aconselhamento de acordo com os algoritmos validados pela Direção-Geral da Saúde; 2. Integração dos casos suspeitos de infeção por SARS-CoV-2 com indicação para vigilância clínica e isolamento no domicílio na plataforma Trace COVID-19, com a informação do nome, número do utente, morada atual e número de telemóvel (e endereço eletrónico, quando disponível); 3. Manter em pronta resposta a funcionalidade de requisição de testes laboratoriais para SARS-CoV-2 para ativação imediata (24 horas) na Fase 2 do Plano da Saúde para o Outono-Inverno 2020/2021; 4. Garantir a atualização da informação relativa aos ADR-C e ADR-SU no *microsite* COVID-19 da DGS; 5. Disponibilização dos meios telemáticos necessários às equipas de saúde das USF/UCSP e USP para o acompanhamento remoto dos doentes com suspeita e confirmação de infeção por SARS-CoV-2 e dos seus contactos.
Centro de Orientação de Doentes Urgentes (**CODU**) e **INEM**, I.P.	1. Proceder à triagem, aconselhamento e encaminhamento para o SNS24 ou ADR-SU nos termos da presente Norma; 2. Garantir a assistência médica pré-hospitalar dos doentes cuja situação clínica seja grave ou crítica; 3. Colaborar na colheita de amostras biológicas para a realização de testes laboratoriais para SARS-CoV2; 4. Colaborar no transporte secundário dos doentes críticos.
ARS, em articulação intersectorial com os **parceiros locais**	1. Definir e garantir a pronta resposta para a eventual instalação de hospitais de campanha e de estruturas residenciais (para onde devem ser encaminhados os doentes com indicação para vigilância clínica e isolamento no domicílio sem condições de habitabilidade e/ou exequibilidade do isolamento no seu domicílio); 2. Nas áreas metropolitanas de Lisboa e Porto: considerar a eventual instalação de ADR-Metropolitanos para ativação imediata na Fase 2 do Plano da Saúde para o Outono-Inverno 2020/2021; 3. Verificar o cumprimento das medidas e ações atribuídas aos laboratórios, especialmente do setor convencionado.
ARS, **Conselhos de Administração das Unidades Locais de Saúde** e **Diretores Executivos dos ACES**, em articulação com	1. Implementar a rede de ADR-C (Anexo 3), com um número e dimensão de ADR-C ajustado aos indicadores demográficos, epidemiológicos e de utilização dos serviços de saúde de cada região e local; 2. Garantir que a rede de ADR-C inclui um circuito/área dedicada para a colheita de amostras biológicas do trato respiratório superior quer para os doentes observados presencialmente na ADR-C quer para doentes com indicação para vigilância clínica e isolamento no domicílio; 3. Mapeamento das ADR-C e comunicação à SGMS e à SPMS sempre que é criada e/ou eliminada uma ADR-C, garantindo a atualização permanente dos dados no SIIP, em conformidade com a Circular Normativa Conjunta n.º

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a ACSS, IP e com a SPMS, EPE / SGMS	01/2020/SGMS/SPMS, nomeadamente, a morada, horários de funcionamento, áreas de influência e e-mail para o encaminhamento do SNS24; 4. Reorganização das equipas de saúde das USF/UCSP de forma a garantir a atividade assistencial COVID-19 e não-COVID-19, de acordo com o Plano da Saúde para o Outono-Inverno 2020-2021; 5. Disponibilização dos meios telemáticos necessários às equipas de saúde das USF/UCSP e USP para o acompanhamento remoto dos doentes com suspeita e confirmação de infeção por SARS-CoV-2 e dos seus contactos; 6. Informação aos cidadãos relativamente aos locais onde estão instaladas as ADR-C, que devem estar bem sinalizadas de forma a garantir a efetiva separação dos circuitos dos doentes com suspeita de infeção respiratória aguda face aos restantes.
ARS, Conselhos de Administração dos Hospitais, Centros Hospitalares e Unidades Locais de Saúde, em articulação com o **GCL-PPCIRA**	1. Implementar um ADR-SU (Anexo 3) em cada serviço de urgência hospitalar, ajustado aos indicadores demográficos, epidemiológicos e de utilização dos serviços de saúde, e de forma articulada com as respostas a nível regional, de acordo com o Plano da Saúde para o Outono-Inverno 2020/2021; 2. Mapeamento das ADR-SU e comunicação à SGMS e à SPMS sempre que é criada e/ou eliminada uma ADR-SU, garantindo a atualização permanente dos dados no SIIP, em conformidade com a Circular Normativa Conjunta n.º 01/2020/SGMS/SPMS, nomeadamente, a morada, horários de funcionamento, áreas de influência e e-mail para o encaminhamento do SNS24; 3. Garantir a efetiva separação dos doentes com suspeita de infeção por SARS-CoV-2 face aos restantes e da implementação das medidas de prevenção e controlo de infeção adequadas; 4. Informar os cidadãos relativamente aos locais onde estão instaladas as ADR-SU, que devem estar bem sinalizadas de forma a garantir a efetiva separação dos circuitos dos doentes com suspeita de infeção respiratória aguda face aos restantes; 5. Criar enfermarias e unidades de cuidados intensivos (UCI) para internamento em *coorte* de doentes com COVID-19, com dimensão adequada à densidade populacional e evolução epidemiológica regional e local; 6. Implementar a resposta da medicina intensiva estabelecida pela Norma n.º 005/2020 da DGS e pela rede Nacional de Especialidade Hospitalar e de Referenciação de Medicina Intensiva.
INFARMED, ARS, Conselhos de Administração dos Hospitais, Centros Hospitalares e Unidades Locais de Saúde	1. Garantir a disponibilização dos equipamentos de proteção individual (EPI) e dispositivos médicos adequados e necessários para a avaliação dos doentes com suspeita e confirmação de infeção por SARS-CoV-2; 2. Garantir a disponibilização e distribuição em tempo clinicamente útil de todos os medicamentos recomendados para a terapêutica dos doentes com COVID-19, nos termos da presente Norma.
ARS, em articulação com	1. Mapear os locais disponíveis para a colheita de amostras e realização de testes laboratoriais, que garantam a obtenção de resultados laboratoriais até 24 horas

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o **INSA**, IP, e a **ACSS**, IP.	desde a sua requisição, dando preferência à colheita de amostras no domicílio e a sistemas *drive-thru*; 2. Enviar ao SNS24, às USF / UCSP / Unidades de Saúde Pública a listagem de locais para colheita e realização de testes laboratoriais, em formato estruturado definido pela SPMS; 3. Comunicar à SGMS e à SPMS da listagem dos postos de colheita e realização de testes laboratoriais, bem como da criação/eliminação de locais para esse fim, garantindo a atualização permanente dos dados no SIIP, em conformidade com a Circular Normativa Conjunta n.º 01/2020/SGMS/SPMS, nomeadamente, a morada, horários de funcionamento, áreas de influência e e-mail para o encaminhamento do SNS24.
Laboratórios e serviços criados ou selecionados (incluindo *drive-thru*) para a colheita e/ou realização de testes laboratoriais	1. Garantir a colheita de amostras no domicílio, ou o agendamento remoto para a colheita de amostras biológicas em áreas dedicadas para o efeito, onde estejam garantidas todas as medidas de prevenção e controlo de infeção, por forma a minimizar as deslocações desnecessárias dos doentes com suspeita de infeção por SARS-CoV-2; 2. Garantir a disponibilização dos resultados dos testes laboratoriais até 12 horas após a sua realização; 3. Notificar todos os resultados de testes laboratoriais para SARS-CoV-2 na plataforma SINAVE*lab* (*área laboratórios*) até 12 horas após a sua realização; 4. Integrar todos os resultados de testes laboratoriais para SARS-CoV-2 no Registo de Saúde Eletrónico (RSE).
Equipas de saúde das **USF / UCSP**	1. Notificar os casos suspeitos na plataforma SINAVEmed (*área médicos*) e na plataforma Trace COVID-19, no prazo máximo de 24 horas desde a data de diagnóstico; 2. Informar o doente das medidas de prevenção e controlo de infeção, nos termos da Orientação n.º 010/2020 da DGS, nomeadamente a necessidade de utilização de máscara cirúrgica nas deslocações (que devem ser evitadas ao máximo possível) para a realização do teste laboratorial; 3. Emitir o Certificado de Incapacidade Temporária para o Trabalho (CIT) aos casos suspeitos/confirmados; 4. Realizar a vigilância clínica dos doentes com suspeita e/ou confirmação de infeção por SARS-CoV-2 com indicação para vigilância clínica e isolamento no domicílio, através da plataforma Trace COVID-19, de acordo com o Anexo 4 da presente Norma.
Equipas de saúde pública das **USP**	1. Determinar o confinamento obrigatório aos casos confirmados de infeção por SARS-CoV-2; 2. Realizar o inquérito epidemiológico, rastreio de contactos e a implementação das medidas de Saúde Pública adequadas, nos termos da Norma n.º 015/2020 da DGS; 3. Determinar o isolamento profilático dos contactos de alto risco de exposição; 4. Articular com as entidades competentes para garantir o encaminhamento dos doentes sem condições de habitabilidade e exequibilidade do isolamento no domicílio para estruturas residenciais (comissão municipal de proteção civil, articulação intersectorial com os parceiros a nível local ou regional).

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ANEXO 2

Adequação da prestação de cuidados aos doentes com suspeita de infeção por SARS-CoV-2

1. Todos os **doentes com suspeita de infeção por SARS-CoV-2 devem ser avaliados quanto a**:

Gravidade da apresentação clínica[2]:
1. **Doença ligeira**: sintomas ligeiros sem evidência de pneumonia ou hipoxemia; 2. **Doença moderada**: pneumonia (febre, tosse, dispneia, taquipneia[i]) mas com saturação periférica de O2 ≥ 90% em ar ambiente, e sem instabilidade hemodinâmica; 3. **Doença grave**: pneumonia e, pelo menos, um dos seguintes critérios[ii]: a. Taquipneia superior a 30 ciclos por minuto; b. Dificuldade respiratória; c. SpO2 inferior a 90% em ar ambiente; d. Instabilidade hemodinâmica; 4. **Doença crítica:** síndrome de dificuldade respiratória aguda com PaO2/FiO2<100 ou choque séptico.

Condições associadas a evolução para COVID-19 grave[2,19,40–45]:
1. Idade superior a 60 anos; 2. Doença crónica: DPOC, asma, insuficiência cardíaca, diabetes, cirrose hepática, doença renal crónica em hemodiálise, drepanocitose; 3. Obesidade; 4. Neoplasia maligna ativa, particularmente sob quimioterapia, radioterapia ou imunoterapia/terapêutica biológica; 5. Imunodepressão, particularmente[46,47]: a. Transplante alogénico de células progenitoras hematopoiéticas há menos de 1 ano ou com doença de enxerto contra hospedeiro; b. Transplante de órgão sólido: pulmonar; ou transplante de outro órgão com tratamento de indução há menos de 6 meses ou com rejeição há menos de 3 meses; c. Terapêutica biológica e/ou prednisolona > 20 mg/dia, ou equivalente, por mais de 14 dias; d. Infeção por VIH sem tratamento e com contagem TCD4^{+} inferior a 200 células/mm^{3}; e. Imunodeficiência primária (síndrome de imunodeficiência combinada grave, agamaglobulinemia ligada X, deficiência do recetor de interferão e síndrome de hiper-IgE).

Condições de habitabilidade e exequibilidade do isolamento no domicílio:

[i] No caso de crianças, avaliar sinais de dificuldade respiratória como tiragem subcostal, supraesternal e intercostal, adejo nasal e taquipneia (definida em ciclos/minuto, conforme a idade em: < 2 meses: ≥ 60 cpm; 2–11 meses: ≥ 50 cpm; 1–5 anos: ≥ 40 cpm).

[ii] Em crianças avaliar ainda existência de gemido, tiragem, cianose central, incapacidade para aleitamento ou hidratação, letargia, alteração do estado de consciência ou movimentos involuntários.

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1. Telefone/Telemóvel facilmente acessível;
2. Termómetro;
3. Quarto separado ou cama individual para o doente;
4. Uso de máscara cirúrgica pelo doente e coabitantes;
5. Acesso a casa de banho, preferencialmente individual;
6. Água e sabão para higiene das mãos e produtos de limpeza doméstica;
7. Cuidador que assegura medicação crónica do doente (de acordo com autonomia do doente);
8. Não residir com pessoas imunodeprimidas ou grávidas.

2. De acordo com a avaliação dos três parâmetros indicados no ponto anterior do presente Anexo, **os doentes com suspeita de infeção por SARS-CoV-2 são encaminhados**, sequencialmente, de acordo com a necessidade de avaliação clínica presencial e de acordo com o local onde é realizado o seguimento clínico dos doentes com COVID-19:

Gravidade da Doença	Condições associadas a COVID-19 grave	Exequibilidade de isolamento	**Avaliação clínica inicial**	**Seguimento clínico**
Ligeira	Não	Sim	Não	**Vigilância clínica e isolamento no domicílio**, através da plataforma Trace COVID-19
		Não	Não	**Vigilância clínica e isolamento em estruturas residenciais**, através da plataforma Trace COVID-19
	Idade > 60 anos Obesidade Doença crónica não descompensada	-	ADR-C	De acordo com avaliação clínica e critérios de internamento
	Doença crónica descompensada Doença renal crónica em hemodiálise Neoplasia maligna ativa Imunossupressão grave	-	ADC-SU	De acordo com avaliação clínica e critérios de internamento
Moderada	-	-	ADR-C	De acordo com avaliação clínica e critérios de internamento
Grave	-	-	ADR-SU	**Internamento Hospitalar**

3. Para o efeito do disposto no número anterior, **os critérios de internamento e de admissão em Unidade de Cuidados Intensivos** são:

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Critérios de Internamento Hospitalar
Todos os doentes com pelo menos um dos seguintes critérios, devem ser internados: 1. Doença grave ou severa, conforme o ponto 1 do presente anexo; 2. Febre (Temperatura ≥ 38.0ºC) persistente com mais de 48h ou reaparecimento de febre após apirexia; 3. Alteração do estado de consciência; 4. Hemoptises; 5. Vómitos persistentes, diarreia grave ou desidratação grave; 6. Leucopenia, linfopenia, ou trombocitopenia, na ausência de outra causa; 7. Nas **crianças**, em particular, existência de rabdomiólise, elevação de marcadores de lesão cardíaca ou alterações eletrocardiográficas ST-T; 8. Existência de doenças crónicas descompensadas ou condições associadas a COVID-19 grave ou a elevada mortalidade, conforme o ponto 2 do presente anexo.

Critérios de Admissão em UCI para Adultos:
Todos os doentes com 1 critério *major* ou ≥ 3 critérios *minor* devem ser admitidos em UCI dedicadas ao tratamento de doentes com COVID-19: 1. Critérios ***major***: a. Choque sético com necessidade de vasopressores; b. Insuficiência respiratória com necessidade de ventilação mecânica invasiva. 2. Critérios ***minor***: a. Frequência respiratória ≥ 30cpm; b. PaO2/FiO2 ≤ 250; c. Pneumonia com envolvimento multilobar; d. Alteração do estado de consciência; e. Ureia ≥ 42mg/dL (BUN ≥ 20mg/dL); f. Leucopénia (< 4000/mm3), na ausência de outra causa; g. Trombocitopénia (< 100000/mm3), na ausência de outra causa; h. Hipotermia (< 35ºC); i. Hipotensão com necessidade de fluidoterapia intensiva.

Critérios de Admissão em UCI para a Idade Pediátrica
Todos os doentes com pelo menos um dos seguintes critérios, devem ser admitidos em UCI dedicadas ao tratamento de doentes com COVID19: 1. Hipoxemia sem resposta à terapêutica convencional com oxigenoterapia suplementar por cateter nasal ou máscara com concentrador de oxigénio; 2. Pneumonia grave com SatO2 < 92% e com frequência respiratória > 70cpm (para pessoas com menos de 12 meses de idade) ou > 50cpm (para pessoas com mais de 12 meses); 3. Insuficiência respiratória com necessidade de ventilação mecânica (invasiva ou não invasiva); 4. Síndrome da Dificuldade Respiratória Aguda; 5. Choque séptico ou instabilidade hemodinâmica, alterações do estado de consciência ou necessidade de suporte de outros órgãos; 6. Critérios de Síndrome Inflamatória Multissistémica[24,25] com agravamento clínico ou laboratorial.

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ANEXO 3

Características das Áreas Dedicadas a Doentes Respiratórios (ADR)

Características[1,2]		**ADR-COMUNIDADE / ACES**
	Físicas	Dispor de áreas de observação reservadas e com circuito exclusivo (separadas das dos doentes sem suspeita); Composta no mínimo por 1 área de receção, 1 área de espera, 2 salas de observação e 1 área de tratamentos, contendo barreiras que permitam separação física entre doentes, e o espaço necessário para a aplicação do distanciamento físico entre doentes; Acesso a instalação sanitária com sabão e toalhetes de papel, para uso exclusivo.
	Sinalética	Sinalização de área reservada a COVID-19, de precauções básicas de controlo de infeção e de risco biológico.
	Equipa	Médico; Enfermeiro; Assistente Operacional; Administrativo; Equipa de Limpeza.
Equipamento e material	Médico - - Cirúrgico	Estetoscópio; Otoscópio; Espátulas; Lanterna; Termómetro de infra-vermelhos; Oxímetro; Esfigmomanómetro; Carro de Emergência com DAE; máscara de oxigenoterapia, fonte de oxigénio (bala) e dispositivos de câmara expansora para administração de terapêutica em solução pressurizada.
	Proteção Individual[i]	Fato de proteção integral ou bata impermeável; Touca; Proteção de calçado; Máscara FFP2; Proteção ocular com proteção lateral; Luvas.
	Outro material	Material de consumo clínico necessário para sala de tratamentos; Sabão; Solução SABA; Toalhetes de papel; Toalhetes impregnados com Peroxido de Hidrogénio acelerado 35%; Dicloroisocanurato de Sódio; Álcool 70%. Kit de colheita de amostras para teste molecular de SARS-CoV-2.
	Outro equipamento	Computador; Impressora; Telefone / Intercomunicador. Caixotes de lixo e sacos de resíduos do tipo III. Contentores de corto-perfurantes.

[1]Ajustadas ao volume de atividade, população abrangida e dimensão e tipologia da unidade de saúde.
[2]Consultar Orientação 015/2020 e Norma 007/2020 da DGS.

[i] No caso da área administrativa ser independente do restante espaço físico da ADR, a Proteção individual compreende máscara cirúrgica, e proteção ocular na ausência de barreiras físicas adequadas. Deve ser evitado qualquer contacto com objetos pessoais dos doentes.

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Características[1,2]		ADR-SU / Serviços de Urgência
	Físicas	Dispor de áreas de observação reservadas e com circuito exclusivo (separadas das dos doentes sem suspeita); Composta no mínimo por 1 área de receção, 1 área de espera e salas para observação e administração de terapêutica, diferenciadas conforme a gravidade clínica dos doentes admitidos, contendo barreiras que permitam separação física entre doentes, e o espaço necessário para a aplicação do distanciamento físico entre doentes; Acesso a instalação sanitária com sabão e toalhetes de papel, para uso exclusivo.
	Sinalética	Sinalização de área reservada a COVID-19, de precauções básicas de controlo de infeção e de risco biológico.
	Equipa	Médico; Enfermeiro; Assistente Operacional; Administrativo; Equipa de Limpeza. Quando aplicável, Técnicos Superiores de Diagnóstico e Terapêutica.
Equipamento e material	Médico - - Cirúrgico	Monitor multiparâmetros (Pressão arterial, traçado ECG, pulso e oximetria); Estetoscópio; Otoscópio; Espátulas; Termómetro de infravermelhos; Carro de Emergência e Reanimação; Acesso a equipamento de ventilação, máscara de oxigenoterapia e fonte de oxigénio e dispositivos de câmara expansora para administração de terapêutica em solução pressurizada.
	Proteção Individual[i]	Fato de proteção integral ou bata impermeável; Touca; Proteção de calçado; Máscara FFP2; Proteção ocular com proteção lateral; Luvas.
	Outro material	Material de consumo clínico necessário para sala de tratamentos; Sabão; Solução SABA; Toalhetes de papel; Toalhetes impregnados com Peroxido de Hidrogénio acelerado 35%; Dicloroisocanurato de Sódio; Álcool 70%; Kit de colheita de amostras para teste molecular de SARS-CoV-2.
	Outro equipamento	Computador; Impressora; Telefone /Intercomunicador; Contentores/Caixotes de lixo e sacos de resíduos do tipo III/IV; Contentores de corto-perfurantes; Carro de recolha de roupa e sacos para roupa.

[1]Ajustadas ao volume de atividade, população abrangida e dimensão e tipologia da unidade de saúde.
[2]Consultar Orientação 015/2020 e Norma 007/2020 da DGS.

[i] No caso da área administrativa ser independente do restante espaço físico da ADR, a Proteção individual compreende máscara cirúrgica, e proteção ocular na ausência de barreiras físicas adequadas. Deve ser evitado qualquer contacto com objetos pessoais dos doentes.

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ANEXO 4

Protocolo para seguimento dos doentes com indicação para vigilância clínica e isolamento em domicílio

A avaliação clínica dos doentes com indicação para isolamento no domicílio, sob vigilância, é assegurada pela equipa de saúde da USF / UCSP, de acordo com o presente protocolo, salvaguardando a dinâmica organizacional de cada unidade.

1. A primeira avaliação telefónica ocorre nas primeiras 24 horas após o contacto com a Linha SNS24 ou a introdução do doente na plataforma *Trace COVID-19*, e é realizada por Médico da equipa de saúde, preferencialmente o Médico de Família do doente.

2. Esta avaliação inclui a:
    a. Avaliação clínica e validação da suspeita de COVID-19;
    b. Prescrição do teste laboratorial para SARS-CoV-2, para todos os casos suspeitos, na plataforma *Exames Sem Papel*;
    c. Notificação do caso de suspeita de infeção na plataforma SINAVE*med* (área *Médicos*);
    d. Exclusão de critérios para avaliação em ADR-SU, nomeadamente:
        i. Febre (≥ 38.0ºC) mantida por mais de 48h ou reaparecimento após apirexia;
        ii. Dificuldade respiratória ou dispneia em repouso ou para pequenos esforços;
        iii. Cianose;
        iv. Toracalgia;
        v. Alteração do estado de consciência;
        vi. Hemoptises;
        vii. Vómitos persistentes ou diarreia grave.
        viii. Comorbilidades indicadas no Anexo 1.
    e. Confirmação da existência de critérios de habitabilidade e exequibilidade de isolamento, no domicílio (Anexo 2), incluindo a informação relativa às medidas de prevenção e controlo de infeção, nos termos da Orientação n.º 010/2020 da DGS, nomeadamente a necessidade de utilização de máscara cirúrgica nas deslocações (que devem ser evitadas ao máximo possível) para a realização do teste laboratorial;
    f. Prescrição de terapêutica sintomática e de suporte, por via eletrónica;
    g. A informação que, em caso de agravamento, deve ser contactada a equipa de saúde da USF / UCSP que o acompanha, a Linha SNS24 ou o 112;
    h. Esclarecimento de dúvidas colocadas pelos doentes, incluindo sobre o CIT;
    i. Articulação com as Autoridades de Saúde. Caso o doente não esteja a cumprir o isolamento no domicílio deve ser contactada a Autoridade de Saúde.

3. Sempre que for considerado clinicamente adequado pode ser programada uma teleconsulta, ou orientado para observação em ADR-Comunidade ou ADR-SU.

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4. A terapêutica prescrita por via eletrónica deverá ser preferencialmente dispensada no domicílio, pelas Farmácias Comunitárias, ou através das respostas organizadas a nível local.

5. Durante o seguimento até à alta clínica o acompanhamento clínico é assegurado por Enfermeiro ou Médico, preferencialmente Enfermeiro ou Médico de Família, da equipa de saúde da USF / UCSP, cumprindo as alíneas do ponto 2 do presente Anexo:
    a. Através de **autoreporte diário**, por parte do doente, na plataforma Trace COVID-19 quando na primeira avaliação telefónica o médico considerar que estão reunidas as condições de qualidade e segurança desta modalidade de seguimento, nomeadamente:
        i. Doentes com COVID-19 assintomática;
        ii. Estabilidade clínica definida pela presença exclusiva de sintomas ligeiros e ausência de sintomas sugestivos de agravamento clínico, ou qualquer critério de referenciação à ADR-SU, nos termos da alínea d do ponto 2 do presente Anexo;
        iii. Capacidade para a utilização das ferramentas tecnológicas para autoreporte de sintomas, por parte do doente, familiar ou cuidador;
        iv. Consentimento para esta modalidade de seguimento clínico.
    b. Através de **avaliação telefónica diária** nas restantes situações.

6. No caso de ser adotada a modalidade de seguimento através da autoreporte de sintomas, nos termos do número anterior:
    a. O registo de sintomas é realizado diariamente pelo doente, através da funcionalidade disponível para o efeito no Registo de Saúde Eletrónico (RSE) ou portal COVID-19 da DGS (https://covid19.min-saude.pt);
    b. A equipa de saúde da USF / UCSP avalia o autoreporte diariamente, através da plataforma *Trace COVID-19,* e garante avaliação telefónica caso o doente não reporte sintomas durante mais de 24 horas;
    c. O seguimento clínico através de autoreporte de sintomas deve ser interrompido sempre que se verificar um agravamento clínico ou qualquer outra situação que o justifique.

7. A equipa de saúde da USF / UCSP garante, por via telefónica, para além da primeira avaliação, a realização de um contacto para a comunicação do resultado do teste e da alta.

8. Aos doentes com infeção confirmada por SARS-CoV-2 que têm a aplicação STAYAWAY COVID[i] instalada deve ser gerado o código de legitimação na plataforma *Trace COVID-19* (https://tracecovid19.min-saude.pt/) para o rastreio de contactos, nos termos da Norma n.º 015/2020 da DGS[i].

[i] Decreto-Lei n.º 52/2020 de 11 de agosto.

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9. As avaliações clínicas resultantes da aplicação deste Anexo são registadas na plataforma *Trace COVID-19* e, sempre que necessário, na plataforma *SClínico*, ou equivalente, como "Consultas Indiretas".

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GRUPO DE ELABORAÇÃO DA NORMA

Primeira Versão e atualizações até 31 de agosto de 2020

Ana Luisa Gomes, Ana Nunes Barata, António Diniz, Benvinda Estela dos Santos, Catarina Damásio, Carla Pereira, Cátia Albino, Célia Oliveira, Diogo Cruz, Elisabete Serrada, Etelvina Calé, Fátima Ventura, Fernando Maltez, Filipe Froes, Graça Lima, Gorete Lopes, Helena Rebelo de Andrade; João Furtado; João Rodrigues, Maria Goreti Silva, Isabel Pires, Leonardo Vinagre, Licínia Sebastião, Maria João Brito, Margarida Tavares, Marta Marcelino, Miguel Cabral, Natália Pereira, Pedro Pacheco, Rita Sá Machado, Rui Nogueira, Sérgio Gomes, Susana Santos, Tiago Soares, Valter Fonseca, Vera Silva.

Foram auscultadas as seguintes instituições ACSS, INFARMED, INSA, SPMS, Administrações Regionais de Saúde, Autoridades de Saúde Regionais, a Ordem dos Enfermeiros, Ordem dos Farmacêuticos e a Ordem dos Médicos.

Presente atualização

Ana Luisa Gomes (coordenação), António Diniz, António Sarmento, Elisabete Serrada, Estevão Santos, Fernando Maltez, Filipe Froes, Gisela Neves, Helena Rebelo de Andrade, Kamal Mansinho, João Furtado (coordenação), João Rodrigues, Maria João Brito, Margarida Tavares, Rui Nogueira, Tiago Soares, Valter Fonseca.

Foi auscultado o Programa Prevenção e Controlo de Infeção e Resistência aos Antimicrobianos (PPCIRA). Foram auscultadas as seguintes instituições ACSS, INEM, INFARMED, INSA, SPMS, Administrações Regionais de Saúde, e as Autoridades de Saúde Regionais.

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NORMA

NÚMERO: 015/2020

DATA: 24/07/2020

Maria da Graça Gregório de Freitas

Digitally signed by Maria da Graça Gregório de Freitas
DN: c=PT, o=Direção-Geral da Saúde, cn=Maria da Graça Gregório de Freitas
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ASSUNTO:	**COVID-19: Rastreio de Contactos**
PALAVRAS-CHAVE:	Coronavírus, SARS-CoV-2, COVID-19, Rastreio de Contactos (Contact Tracing), Investigação Epidemiológica
PARA:	Sistema de Saúde
CONTACTOS:	dspdps@dgs.min-saude.pt

A COVID-19 foi reconhecida pela Organização Mundial de Saúde como pandemia no dia 11 de março de 2020. Neste contexto, foram adotadas várias medidas para conter a expansão da infeção por SARS-CoV-2. Considerando a evolução epidemiológica foi determinado o início gradual do levantamento das medidas de confinamento.

De acordo com a Organização Mundial de Saúde (OMS), a Comissão Europeia e o Centro Europeu para a Prevenção e Controlo de Doenças (ECDC) um efetivo **rastreio de contactos** (identificação, avaliação do risco e implementação de medidas) é um elemento chave para a deteção precoce de casos e limitação da propagação da COVID-19.

Esta estratégia ("*Test-Track-Trace*") tem vindo a ser adotada em Portugal a três níveis: a) identificação precoce dos casos através de uma utilização adequada de testes laboratoriais; b) seguimento clínico adequado (com utilização do sistema de informação disponível na plataforma Trace COVID-19) de todos os casos de infeção por SARS-CoV-2, quer em ambulatório, quer em meio hospitalar; c) efetiva identificação e vigilância de contactos dos casos confirmados, coordenado pelas autoridades de saúde.

O **rastreio de contactos** consiste em três passos[1]:

a) Identificação de todas as pessoas (contactos) que estiveram potencialmente expostas a gotículas respiratórias ou secreções de um caso de COVID-19;
b) Avaliação dos contactos com estratificação de risco, através da investigação e comunicação com os contactos identificados;
c) Implementação de medidas, incluindo o isolamento profilático e a vigilância (seguimento e a monitorização regular dos contactos relativamente à sua sintomatologia).

[1] European Centre for Disease Prevention and Control. Contact tracing: public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union – second update, 8 April 2020. Stockholm: ECDC; 2020.

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Assim, nos termos da alínea a) do n.º 2 do art. 2.º do Decreto Regulamentar n.º 14/2012, de 26 de janeiro, a Direção-Geral da Saúde emite a seguinte Norma:

Definição de Contacto

1. Um contacto é uma pessoa que esteve exposta a um caso de COVID-19, ou a material biológico infetado com SARS-CoV-2, dentro do período de transmissibilidade.

2. Para efeitos do rastreio de contactos, o período de transmissibilidade estende-se desde 48 horas antes da data de início de sintomas do caso de COVID-19 sintomático ou da data da colheita do produto biológico do teste laboratorial do caso de COVID-19 assintomático até ao dia em que é estabelecida a cura do caso, definida nos termos da Normas 004/2020 e 010/2020 da DGS.

3. O risco de contrair infeção por SARS-CoV-2 é dependente do nível de exposição. Os contactos de caso de COVID-19 são classificados, de acordo com o seu nível de exposição, em exposição de alto risco e de baixo risco, nos termos do Anexo 1.

4. A estratificação dos contactos pelo risco de exposição determina o tipo de vigilância e de medidas a implementar.

5. A implementação das medidas da presente Norma não se aplica a pessoas com história prévia de infeção por SARS-CoV-2, confirmada laboratorialmente, que tenham cumprido os critérios de cura, estabelecidos nas Normas 004/2020 ou 010/2020 da DGS.

Abordagem de Contacto

6. Após a identificação de um caso de COVID-19, deve ser assegurada a investigação epidemiológica detalhada pela Autoridade de Saúde, apoiada pela Unidade de Saúde Pública e, com base na avaliação de risco, aplicado o conjunto de medidas considerado apropriado.

7. Os procedimentos de investigação epidemiológica, em particular o rastreio de contactos, devem ser realizados o mais precocemente possível, preferencialmente nas 12 horas seguintes à identificação do caso, e independentemente da forma como se tomou conhecimento da existência do caso de COVID-19.

8. Os contactos identificados durante a investigação epidemiológica, classificados de acordo com o Anexo 1, devem ser introduzidos na área "Lista de Contactos" do SINAVE e na plataforma Trace COVID-19 (https://tracecovid19.min-saude.pt/).

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9. Devem ser igualmente investigadas todas as pessoas que tenham sido consideradas como eventuais "contactos" pelo SNS24, ou por outros profissionais de saúde, e inseridas, como tal, na plataforma Trace COVID-19 (em "vigilância ativa" até à avaliação pela Autoridade de Saúde). Para o efeito, a Autoridade de Saúde, apoiada pela Unidade de Saúde Pública, deve recorrer à plataforma Trace COVID-19, executando as tarefas diárias geradas pela plataforma para os contactos.

10. Se o caso de COVID-19 identificado esteve a bordo de uma aeronave ou navio dentro do período de transmissibilidade, deve ser dado conhecimento à Autoridade de Saúde do aeroporto/aeródromo onde a aeronave aterrou ou do porto marítimo onde o navio atracou.

11. Se durante o rastreio de contactos forem identificados cidadãos, portugueses ou de outras nacionalidades, que não se encontrem em Portugal, a Autoridade de Saúde Regional deve informar o Centro de Emergências em Saúde Pública da DGS (cesp@dgs.min-saude.pt), para partilha, sempre que necessário e de acordo com a legislação aplicável, da informação relevante, com as Autoridades de Saúde dos respetivos países.

12. Todos os contactos devem ser informados, pela Autoridade de Saúde territorialmente competente, das medidas a adotar, de acordo com a avaliação de risco e a presente Norma.

13. Se durante a identificação de contactos for detetada sintomatologia compatível com COVID-19, a Autoridade de Saúde responsável pelo rastreio de contactos deve iniciar os procedimentos de Caso Suspeito, de acordo com a presente Norma.

14. Para a efetiva implementação dos procedimentos da presente Norma, a Autoridade de Saúde pode solicitar o apoio de outros elementos da Unidade de Saúde Pública, ou outros profissionais de fora desta, que considere necessários, distribuindo-lhes algumas das tarefas, nomeadamente a vigilância diária dos contactos.

Contactos com Exposição de Alto Risco

15. Um contacto classificado como tendo exposição de alto risco, nos termos do Anexo 1 fica sujeito a:
    a. Vigilância ativa durante 14 dias, desde a data da última exposição;
    b. Determinação de isolamento profilático, no domicílio ou outro local definido a nível loca, pela Autoridade de Saúde, até ao final do período de vigilância ativa, de acordo com o modelo dos Despachos n.º 2836-A/2020 e/ou n.º 3103-A/2020[2].

[2] http://www.seg-social.pt/documents/10152/16819997/GIT_70.docx/e6940795-8bd0-4fad-b850-ce9e05d80283

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16. A vigilância ativa tem como objetivo detetar precocemente o aparecimento de sintomas compatíveis com COVID-19 e inclui:
    a. O contacto diário, telefónico ou com recurso a outros meios telemáticos (nomeadamente a funcionalidade de auto-reporte, disponível no Registo de Saúde Eletrónico ou no portal COVID-19 [https://covid19.min-saude.pt]), pelas Autoridades de Saúde, ou profissionais a quem tenha sido atribuída essa tarefa, supervisionados pela Autoridade de Saúde;
    b. O registo na plataforma Trace COVID-19.

17. O contacto de alto risco deve ser informado das seguintes medidas a adotar durante o período de vigilância ativa:
    a. Automonitorizar diariamente sintomas compatíveis com COVID-19, através da funcionalidade de auto-reporte, disponível no Registo de Saúde Eletrónico ou no portal COVID-19 e cujos dados migram para a plataforma Trace COVID-19, de acordo com a indicação da Autoridade de Saúde, se esta considerar que estão reunidas condições para um reporte fidedigno;
    b. Medir e registar a temperatura corporal, duas vezes por dia;
    c. Estar contactável;
    d. Implementar rigorosamente as medidas de higiene das mãos e etiqueta respiratória;
    e. Estar em isolamento/confinamento obrigatório, nos termos definidos na legislação em vigor, no domicílio ou outro local designado para o efeito, e em cumprimento das regras e medidas definidas na Orientação 010/2020 da DGS;
    f. Contactar, preferencialmente, a Autoridade de Saúde responsável pela vigilância ativa (através do número telefónico fornecido por esta ao utente, no primeiro contacto), ou o SNS24, se surgirem sintomas compatíveis com COVID-19.

18. A Autoridade de Saúde Local, para efeitos de fiscalização do cumprimento do confinamento obrigatório, previsto no quadro legal em vigor, deve remeter informação relativa às pessoas com determinação de confinamento/isolamento profilático para as forças e serviços de segurança da área de residência, utilizando os circuitos de articulação entre as Autoridades de Saúde e as forças e serviços de segurança.

19. Nos contactos de alto risco pode ser considerada a realização de teste laboratorial molecular (RT-PCR ou rRT-PCR), de acordo com a avaliação do risco pelas Autoridades de Saúde, especialmente nas situações de surtos/clusters[3,4] e em pessoas com exposição prolongada

[3] **Surto**: é uma situação de doença com uma incidência superior à esperada numa região, comunidade ou local bem definido; **Cluster (Aglomerado)**: é um agregado de casos com relação espacial e/ou temporal, percecionado como superior ao esperado pelo acaso (adaptado de: *Dictionary of Epidemiology, 6th Edition* Edited by Miquel Porta. Oxford University Press, New York, New York).

[4] Nomeadamente as pessoas de risco identificadas na Norma 004/2020 da DGS, incluindo os residentes em RNCCI, UCCI e ERPI, nos termos da Orientação 009/2020 da DGS e os doentes com Doença Renal Crónica em Hemodiálise, nos termos da Norma 008/2020 da DGS.

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ao caso (como, por exemplo, coabitantes), sobretudo, em espaços fechados e pouco ventilados.

20. Nas situações indicadas no ponto anterior, o teste laboratorial para SARS-CoV-2 deve ser realizado, aos contactos em isolamento profilático, entre o 7.º-8.º dia[5] após a última exposição de risco, ou no momento da identificação do contacto em situação de exposição mantida e continuada (por exemplo, diária) ao caso confirmado. Se:
    a. Resultado positivo: Norma 010/2020 da DGS.
    b. Resultado negativo: mantem-se a vigilância ativa e o isolamento profilático, de acordo com os pontos 15 a 187 da presente Norma.

21. No decurso do período de vigilância ativa, se forem identificados sintomas compatíveis com COVID-19, a Autoridade de Saúde deve iniciar os procedimentos de Caso Suspeito, de acordo com a presente Norma.

Contactos com Exposição de Baixo Risco

22. Um contacto classificado como tendo exposição de baixo risco, nos termos do Anexo 1, fica sujeito a vigilância passiva durante 14 dias, desde a data da última exposição.

23. O contacto de baixo risco deve ser informado das seguintes medidas a adotar durante o período de vigilância passiva:
    a. Automonitorizar diariamente sintomas compatíveis com COVID-19;
    b. Medir e registar a temperatura corporal, duas vezes por dia;
    c. Implementar rigorosamente as medidas de distanciamento, higiene das mãos e etiqueta respiratória e a utilização de máscara de acordo com a Orientação 019/2020 e Informação 009/2020 da DGS;
    d. Não frequentar locais com aglomerações de pessoas, mantendo a atividade laboral e assegurando o cumprimento da alínea anterior;
    e. Autoisolar-se e contactar a Autoridade de Saúde responsável pela vigilância passiva (através do número telefónico fornecido por esta ao utente, no primeiro contacto), ou o SNS24, se surgirem sintomas compatíveis com COVID-19.

24. A informação relativa à automonitorização prevista no número anterior da presente Norma deve ser registada, pelo utente, no Registo de Saúde Eletrónico ou no portal COVID-19, através da funcionalidade de auto-reporte, cuja informação migra para a plataforma Trace COVID-19. Na impossibilidade de registo eletrónico de sintomas, o doente deve optar por um registo pessoal.

[5] O período mediano de incubação da infeção por SARS-CoV-2 é de 5-6 dias, pelo que a realização de teste laboratorial após este período (ao 7.º-8.º dia) parece diminuir a probabilidade de um resultado negativo ser um "falso negativo".

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25. No decurso do período de vigilância passiva, se forem identificados sintomas compatíveis com COVID-19, a Autoridade de Saúde é alertada, através da plataforma Trace COVID-19, ou pelo utente, e deve confirmar que foram iniciados, ou iniciar, os procedimentos de Caso Suspeito.

Caso Suspeito Detetado Durante a Identificação ou Vigilância de Contactos

26. A Autoridade de Saúde que deteta o aparecimento de sintomatologia compatível com COVID-19 deve avaliar, por via telefónica, o caso suspeito e encaminhá-lo, de acordo com a gravidade do quadro clínico e os procedimentos definidos na Norma n.º 004/2020 da DGS, para:
    a. Autocuidado, em isolamento no domicílio;
    b. Avaliação clínica em Área Dedicada COVID-19 nos Cuidados de Saúde Primários (ADC-COMUNIDADE) da área de residência;
    c. Avaliação clínica em Área Dedicada COVID-19 nos Serviços de Urgência do SNS (ADC-SU);
    d. INEM, através do 112.

27. O caso suspeito deve realizar teste laboratorial para SARS-CoV-2, de acordo com a Orientação 015/2020 da DGS, sendo o teste prescrito pela Autoridade de Saúde para os doentes encaminhados para autocuidado ou pelo médico que avalia a pessoa no ADC-Comunidade ou no ADC-SU.

28. O caso suspeito com indicação para autocuidado, em isolamento no domicílio, é vigiado pelas equipas das USF/UCSP, de acordo com a Norma 004/2020, até ser conhecido resultado do teste laboratorial.

29. O caso suspeito com teste laboratorial positivo mantém o seguimento clínico pelas equipas das USF/UCSP, de acordo com a Norma 004/2020. Neste caso, a Autoridade de Saúde deve iniciar os procedimentos de caso confirmado, incluindo a respetiva investigação epidemiológica e o rastreio de contactos, de acordo com a presente Norma.

30. O caso suspeito com teste laboratorial negativo mantém a vigilância e as medidas previamente instituídas pela Autoridade de Saúde, de acordo com a presente Norma, sem prejuízo da avaliação e seguimento adequados à situação clínica, pelo seu médico assistente.



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ANEXO 1: Classificação de contactos de COVID-19[6]

A classificação do risco de exposição dos contactos é da responsabilidade da Autoridade de Saúde, de acordo com os critérios definidos neste anexo.

A Autoridade de Saúde, na avaliação individual de risco (caso a caso), pode considerar como contacto outras situações, assim como alterar a classificação do risco de exposição do contacto, nomeadamente quando exista utilização de equipamentos de proteção individual ou máscara.

Exposição de Alto Risco

Pessoa com:

- Contacto frente a frente com um caso de COVID-19 a uma distância de menos de 2 metros e durante 15 minutos ou mais;
- Contacto físico direto com um caso de COVID-19;
- Contacto direto desprotegido com secreções contaminadas de um caso de COVID-19;
- Contacto em ambiente fechado com um caso de COVID-19 (ex. coabitação, sala de aula, sala de reuniões, sala de espera) durante 15 minutos ou mais;
- Viagem com caso de COVID-19:
    - Numa aeronave em que:
        - Esteja sentada até 2 lugares para qualquer direção em relação ao caso (2 lugares a toda a volta do caso);
        - Seja companheira de viagem;
        - Efetue prestação direta de cuidados ao caso;
        - Seja tripulante de bordo e sirva a secção do caso;
        - Se caso com sintomatologia grave ou com grande movimentação dentro da aeronave, todas as pessoas podem ser consideradas como contacto;
    - Num navio em que:
        - Seja companheira de viagem;
        - Partilhe a mesma cabine;
        - Efetue prestação direta de cuidados;
        - Seja tripulante de bordo e sirva a cabine do caso;
        - Aplicam-se também as condições descritas nos pontos acima não referentes às viagens;
    - Em qualquer outro meio de transporte que:
        - Não tenha boa ventilação;
        - Não efetue paragens frequentes com abertura de portas;
        - Não tenha redução da lotação máxima;

[6] European Centre for Disease Prevention and Control. Contact tracing: public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union – second update, 8 April 2020. Stockholm: ECDC; 2020.

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- Exposição associada a cuidados de saúde, com prestação direta, desprotegida, de cuidados a casos de COVID-19 (isto é, sem uso de EPI adequado à atividade assistencial respetiva, de acordo com a Norma 007/2020 ou a Orientação 019/2020, ou quando houver indícios de utilização/remoção incorreta);
- Contacto desprotegido, em ambiente laboratorial ou locais de colheita, com produtos biológicos infetados com SARS-CoV-2.

Exposição de Baixo Risco

Pessoa com:

- Contato frente a frente com um caso de COVID-19 a uma distância de menos de 2 metros e durante menos de 15 minutos;
- Contacto em ambiente fechado com caso de COVID-19 durante menos de 15 minutos ou contacto protegido durante 15 minutos ou mais;
- Viagem com caso de COVID-19 em qualquer meio de transporte, com exceção dos referidos na exposição de alto risco;
- Contacto esporádico (em movimento/circulação) com caso de COVID-19;
- Exposição associada a cuidados de saúde, sem prestação direta de cuidados a casos de COVID-19 sem utilização de EPI;
- Exposição associada a cuidados de saúde, com prestação direta, protegida, de cuidados a casos de COVID-19 (isto é, com uso de EPI adequado à atividade assistencial respetiva, de acordo com a Norma 007/2020 ou a Orientação 019/2020).

A duração do contacto com um caso de COVID-19 aumenta o risco de transmissão, pelo que é definido um limite de 15 minutos, de acordo com as recomendações internacionais, por questões de organização e exequibilidade.

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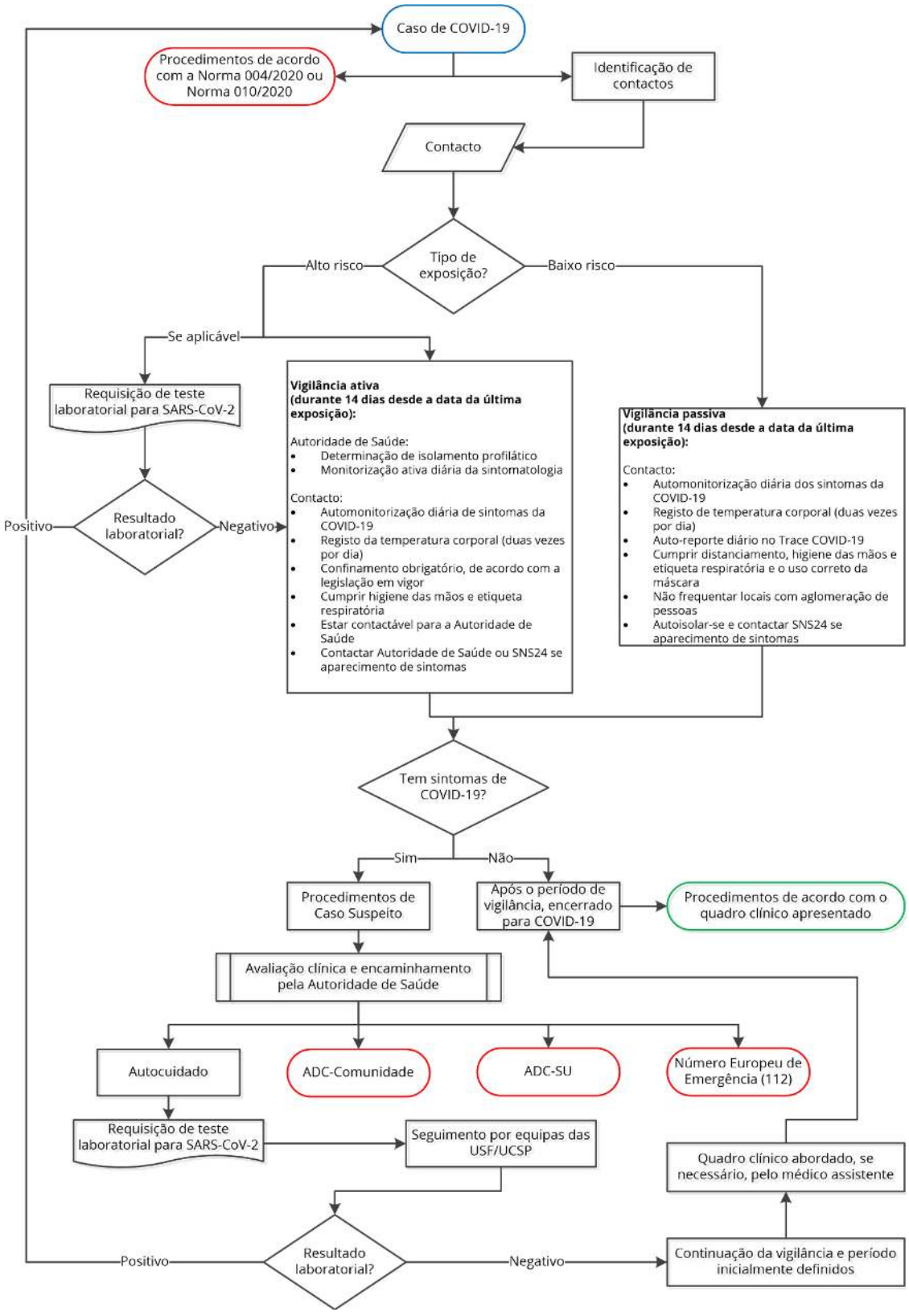
ANEXO 2: Fluxo de abordagem de acordo com a classificação do contacto



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NORMA

Graça Freitas

Digitally signed by Graça Freitas
DN: c=PT, title=Diretora-Geral da Saúde, ou=Direção, o=Direção-Geral da Saúde, cn=Graça Freitas
Date: 2020.11.09 11:41:34 Z

NÚMERO: 020/2020

DATA: 09/11/2020

ASSUNTO:	**COVID-19: Definição de Caso de COVID-19**
PALAVRAS-CHAVE:	COVID-19; SARS-CoV-2; Caso confirmado; Caso possível; Caso provável; Critérios; Investigação Epidemiológica
PARA:	Sistema de Saúde
CONTACTOS:	sinave@dgs.min-saude.pt

A Lei n.º 81/2009, de 21 de agosto instituiu um sistema de vigilância em saúde pública, que identifica situações de risco, recolhe, atualiza, analisa e divulga os dados relativos a doenças transmissíveis e outros riscos em saúde pública que devem ser abrangidos pela rede de informação e comunicação estabelecida pelo Sistema Nacional de Informação de Vigilância Epidemiológica (SINAVE), competindo à Diretora-Geral da Saúde definir quais as doenças transmissíveis de notificação obrigatória e outros riscos para a saúde pública e que devem ser abrangidos pela rede de informação e comunicação estabelecida pelo SINAVE.

Decorridos mais de sete meses desde o reconhecimento da COVID-19 como pandemia pela Organização Mundial de Saúde importa atualizar a Definição de Caso de infeção por SARS-CoV-2/ COVID-19, considerando o atual conhecimento científico.

Assim, ao abrigo do disposto nas alíneas b), c), d) e e) do art. 9.º da Lei n.º 81/2009, de 21 de agosto e nos termos da alínea a) do n.º 2 do art. 2.º do Decreto Regulamentar n.º 14/2012, de 26 de janeiro, a Direção-Geral da Saúde emite a seguinte Norma:

1. É revogada a Orientação 002A/2020 da DGS.

2. **Critérios para a Definição de Caso de COVID-19**:

   a. **Critérios clínicos:** Qualquer pessoa que apresente, pelo menos, um dos seguintes critérios:
      i. Tosse de novo ou agravamento do padrão habitual;
      ii. Febre (temperatura corporal ≥ 38,0ºC) sem outra causa atribuível;
      iii. Dispneia / dificuldade respiratória sem outra causa atribuível;
      iv. Anosmia de início súbito;
      v. Disgeusia ou ageusia de início súbito.

   b. **Critérios epidemiológicos:** Qualquer pessoa que apresente, pelo menos, um dos seguintes critérios nos 14 dias antes do início de sintomas:

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i. Contacto com um caso confirmado de COVID-19;
ii. Residente ou trabalhador numa instituição onde se encontrem pessoas em situações vulneráveis (Estrutura Residencial para Pessoas Idosas, Estabelecimento prisional, Abrigo, Casa de Acolhimento ou instituição equiparada) e onde existe transmissão documentada de COVID-19;
iii. Exposição laboratorial não protegida a material biológico infetado/contendo com SARS-CoV-2.

c. **Critérios imagiológicos:**
   i. Na radiografia do tórax: hipotransparências difusas, de contornos irregulares, com distribuição bilateral periférica e/ou subpleural, com predomínio nos lobos inferiores, e/ou consolidação com distribuição periférica e basal.
   ii. Na tomografia computorizada do tórax: hipodensidades em vidro despolido, com uma distribuição periférica e subpleural; consolidações segmentares multifocais, com distribuição predominante subpleural ou ao longo dos feixes broncovasculares; consolidação com sinal de halo invertido, sugerindo pneumonia organizativa.

d. **Critérios laboratoriais:**
   i. Deteção de ácido nucleico (RNA) de SARS-CoV-2 através de teste molecular de amplificação de ácidos nucleicos (TAAN) em pelo menos uma amostra respiratória;
   ii. Deteção de antigénio de SARS-CoV-2 através de Testes Rápidos de Antigénio (TRAg) em pelo menos uma amostra respiratória, realizados nos termos da Norma 019/2020 da DGS.

3. **Classificação do Caso de COVID-19**:

a. **Caso Possível**: pessoa que preencha os critérios clínicos.

b. **Caso Provável:** pessoa que preencha um dos seguintes critérios:
   i. Critérios clínicos e critérios epidemiológicos;
   ou
   ii. Critérios clínicos e critérios imagiológicos.

c. **Caso Confirmado:** pessoa que preencha os critérios laboratoriais.

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Special Article

The Surviving Sepsis Campaign Bundle: 2018 Update

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INTRODUCTION

The "sepsis bundle" has been central to the implementation of the Surviving Sepsis Campaign (SSC) from the first publication of its evidence-based guidelines in 2004 through subsequent editions (1–6). Developed separately from the guidelines publication by the SSC, the bundles have been the cornerstone of sepsis quality improvement since 2005 (7–11). As noted when they were introduced, the bundle elements were designed to be updated as indicated by new evidence and have evolved accordingly. In response to the publication of "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016" (12, 13), a revised "hour-1 bundle" has been developed and is presented below (**Fig. 1**).

The compelling nature of the evidence in the literature, which has demonstrated an association between compliance with bundles and improved survival in patients with sepsis and septic shock, led to the adoption of the SSC measures by the National Quality Forum (NQF) and subsequently both by the New York State (NYS) Department of Health (14) and the Centers for Medicare and Medicaid Services (CMS) (15) in the USA for mandated public reporting. The important relationship between the bundles and survival was confirmed in a publication from this NYS initiative (16).

Paramount in the management of patients with sepsis is the concept that sepsis is a medical emergency. As with polytrauma, acute myocardial infarction, and stroke, early identification and appropriate immediate management in the initial hours after development of sepsis improves outcomes (7–11, 14, 16–21). The guidelines state that these patients need urgent assessment and treatment, including initial fluid resuscitation while pursuing source control, obtaining further laboratory results, and attaining more precise measurements of hemodynamic status. A guiding principle is that these complex patients need a detailed initial assessment and then ongoing re-evaluation of their response to treatment. The elements of the 2018 bundle, intended to be initiated within the first hour, are listed in **Table 1** and presented in the following. Consistent with previous iterations of the SSC sepsis bundles, "time zero" or "time of presentation" is defined as the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review. Because this new bundle is based on the 2016 Guidelines publication, the guidelines themselves should be referred to for further discussion and evidence related to each element and to sepsis management as a whole.

HOUR-1 BUNDLE

The most important change in the revision of the SSC bundles is that the 3-h and 6-h bundles have been combined into a single "hour-1 bundle" with the explicit intention of beginning resuscitation and management immediately. We believe this reflects the clinical reality at the bedside of these seriously ill patients with sepsis and septic shock—that clinicians begin treatment immediately, especially in patients with hypotension, rather than waiting or extending resuscitation measures over a longer period. More than 1 hour may be required for resuscitation to be completed, but initiation of resuscitation and treatment, such as obtaining blood for measuring lactate and blood cultures, administration of fluids and antibiotics, and in the case of life-threatening hypotension, initiation of vasopressor therapy, are all begun immediately. It is also important to note that there are no published studies that have evaluated the efficacy in important subgroups, including burns and immunocompromised patients. This knowledge gap needs to be addressed in future studies specifically targeting these subgroups. The elements included in the revised bundle are taken

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- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

**"Time zero" or "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.*

Figure 1. Hour-1 Surviving Sepsis Campaign Bundle of Care.*

from the Surviving Sepsis Campaign Guidelines, and the level of evidence in support of each element can be seen in Table 1 (12, 13). We believe the new bundle is an accurate reflection of actual clinical care.

Measure Lactate Level

While serum lactate is not a direct measure of tissue perfusion (22), it can serve as a surrogate, as increases may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess beta-adrenergic stimulation, or other causes associated with worse outcomes (23). Randomized controlled trials have demonstrated a significant reduction in mortality with lactate-guided resuscitation (24–28).

If initial lactate is elevated (> 2mmol/L), it should be remeasured within 2–4 h to guide resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (24).

Obtain Blood Cultures Prior to Antibiotics

Sterilization of cultures can occur within minutes of the first dose of an appropriate antimicrobial (29, 30), so cultures must be obtained before antibiotic administration to optimize the identification of pathogens and improve outcomes (31, 32). Appropriate blood cultures include at least two sets (aerobic and anaerobic). Administration of appropriate antibiotic therapy should not be delayed in order to obtain blood cultures.

Administer Broad-Spectrum Antibiotics

Empiric broad-spectrum therapy with one or more intravenous antimicrobials to cover all likely pathogens should be started immediately (21) for patients presenting with sepsis or septic shock. Empiric antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established, or discontinued if a decision is made that the patient does not have infection. The link between early administration of antibiotics for suspected infection and antibiotic stewardship remains an essential aspect of high-quality sepsis management. If infection is subsequently proven not to exist, then antimicrobials should be discontinued.

Administer IV Fluid

Early effective fluid resuscitation is crucial for the stabilization of sepsis-induced tissue hypoperfusion or septic shock. Given the urgent nature of this medical emergency, initial fluid resuscitation should begin immediately upon recognizing a patient with sepsis and/or hypotension and elevated lactate, and completed within 3 hours of recognition. The guidelines recommend this should comprise a minimum of 30 mL/kg of intravenous crystalloid fluid. Although little literature includes controlled data to support this volume, recent interventional studies have described this as usual practice in the early stages of resuscitation, and observational evidence is supportive (7, 8). The absence of any clear benefit following the administration of colloid compared with crystalloid solutions in the combined subgroups of sepsis, in conjunction with the expense of albumin, supports a strong recommendation for the use of crystalloid solutions in the initial resuscitation of patients with sepsis and septic shock. Because some evidence indicates that a sustained positive fluid balance during ICU stay is harmful (33–37), fluid administration beyond initial resuscitation requires careful assessment of the likelihood that the patient remains fluid responsive.

TABLE 1. Bundle Elements With Strength of Recommendations and Under-Pinning Quality of Evidence (12, 13)

Bundle Element	Grade of Recommendation and Level of Evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

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Apply Vasopressors

Urgent restoration of an adequate perfusion pressure to the vital organs is a key part of resuscitation. This should not be delayed. If blood pressure is not restored after initial fluid resuscitation, then vasopressors should be commenced within the first hour to achieve mean arterial pressure (MAP) of ≥ 65 mm Hg. The physiologic effects of vasopressors and combined inotrope/vasopressor selection in septic shock are outlined in a large number of literature reviews (38–47).

SUMMARY

Previous iterations of the sepsis bundle were introduced as a means of providing education and improvement related to sepsis management. The literature supports the use of sepsis bundles for improving outcomes in patients with sepsis and septic shock. This new sepsis "hour-1 bundle," based on the 2016 guidelines, should be introduced to emergency department, floor, and ICU staff as the next iteration of ever-improving tools in the care of patients with sepsis and septic shock as we all work to lessen the global burden of sepsis.

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Physical Training Injuries and Interventions for Military Recruits

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ABSTRACT Low physical fitness levels are associated with increased musculoskeletal injury risk and attrition among military recruits. The authors review physical fitness trends, injury risk factors, and Department of the Army initiatives to address recruit fitness, injuries, and attrition. Initiatives include the Fitness Assessment Program, which reduced injury risk and attrition among low-fit trainees, and the Assessment of Recruit Motivation and Strength, which enabled the Army to enlist individuals exceeding body composition accession standards without increasing attrition. Physical Readiness Training (PRT) is the Army's primary initiative to address training-related injuries and attrition. PRT's inherent injury control and exercise progression components are designed to address low fitness levels across entry-level training. PRT has been shown to decrease injury rates, but low-fit recruits remain at increased risk regardless of program design. The authors recommend resuming pre-enlistment fitness screening and fitness programming before low-fit recruits begin entry-level training. The decision whether to screen for fitness before beginning entry-level training could be based upon the existing recruiting environment in terms of applicant supply and the demand for recruits. However, the Army should anticipate increased injury and attrition rates when discontinuing screening and/or fitness programming for low-fit recruits.

INTRODUCTION

Initial Military Training (IMT)-related musculoskeletal injuries significantly impact the Department of the Army; approximately 25% of male and 50% of female recruits sustain one or more injuries during Basic Combat Training (BCT).[1] These injuries consistently account for more than 80% of disability-related medical discharges among first-year recruits.[2,3] The associated cost during fiscal year (FY) 2005 was estimated at $57,500 per discharged recruit.[4] Assembled by the National Academies, the National Research Council Committee on the Youth Population and Military Recruitment has highlighted entry-level training-related injuries as "the single most significant medical impediment to military readiness."[5]

The authors will review the impact of physical fitness on musculoskeletal injury risk and provide a rationale for resuming pre-enlistment fitness screening and fitness programming before low-fit recruits begin BCT. The focus of this review is overuse injuries, which account for 70 to 80% of IMT-related musculoskeletal injuries and thus more than half of all disability discharges among first-year recruits.[2,3,6,7] Unless noted, the authors will use the term "training-related injury" when discussing IMT-related overuse musculoskeletal injuries.

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PHYSICAL FITNESS AND TRAINING-RELATED INJURY RISK

Researchers have identified multiple risk factors for training-related injury (Table I). Physical fitness figures prominently among these factors. Fitness components include aerobic endurance, muscular endurance, muscular strength, body composition, flexibility, mobility, and dynamic balance.[10,11] Each component impacts risk to a varying degree.

Aerobic fitness is typically assessed by timed running performance or maximal or peak oxygen consumption (VO_{2max} or VO_{2peak}). Low aerobic fitness is the component most strongly and consistently associated with increased injury risk.[8,12] Muscular endurance measures ability to repeatedly move a load. Low muscular endurance has consistently been associated with increased risk, although less so than aerobic fitness.[13,14] Muscular strength measures maximal force generation capability. The association between strength and injury risk is inconsistent; strength asymmetries (left-to-right-side differences) have been associated with increased risk.[13–16]

Body composition or body fatness can be directly estimated by hydrostatic weighing, dual-energy X-ray absorptiometry, bioelectrical impedance, skinfold thickness, and circumferential measures. The Army uses specified anatomic circumferential measurements to estimate body fat percentage. Body mass index (BMI) frequently serves as a proxy or indirect measure to predict body composition. BMI is a weight–height ratio expressed as weight in kilograms divided by height in meters squared (kg/m^2); it does not distinguish between fat and fat-free tissues such as bone and muscle. BMI generally serves as a fair proxy for body fat, excluding those with high muscle mass.

The association between BMI and injury risk is inconsistent.[13] A bimodal relationship may exist; high and low extremes of BMI appear to be at increased risk.[14,17] The

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TABLE I. Risk Factors for Training-Related Injury[1,5,8,9]

Demographic Factors
Female Gender[a]
Caucasian Race
Age > 24 years
Anatomical Factors
Rigid, High Arched Foot
Flexible, flat foot[b]
Knee Q Angle > 15 degrees
Genu Valgus
Decreased Ankle Dorsiflexion
Increased Rearfoot Inversion
Physical Fitness Factors
Low Aerobic Fitness
Extremes of Flexibility
Low Muscular Endurance
Low Muscular Strength
Extremes of BMI and Composition
Behavioral Factors
Cigarette Smoking
Low Levels of Physical Activity/Exercise/Running Before IMT
Medical Factors
History of Musculoskeletal Injury (esp. Ankle Sprain)
—

[a]Conflicting reports concerning whether female risk is equal to that of males when matched for aerobic fitness.
[b]Conflicting reports concerning association with training-related injury.

Accession Medical Standards Analysis & Research Activity (AMSARA), Walter Reed Army Institute of Research has identified enlistees with BMI < 18 and those with BMI > 33 as being at greatest risk for medical discharge.[18] AMSARA has recommended that body composition interventions target underweight and obese Soldiers.[18]

More important than body composition alone is the interaction between BMI and fitness level with injury risk. Recruits with both low aerobic fitness and low BMI appear to be at greatest risk.[19] Low BMI could indicate lesser muscle or bone mass; underweight individuals may lack the strength required for strenuous tasks including standard load bearing.[19,20]

Training Circular 3-22.20 (Army Physical Readiness Training) defines mobility as "movement proficiency" or functional strength and endurance application.[11] Fundamental movement pattern components include dynamic balance, strength, and flexibility.[16] Flexibility extremes and asymmetries appear to increase injury risk.[8,16,21] Researchers have associated Functional Movement Screen performance deficits with increased risk (although not overuse injury risk) among professional football players and Marine officer candidates.[16,22] Similarly, decreased or asymmetrical balance per Star Excursion Balance Test performance has been associated with increased lower extremity injury risk among basketball players.[23]

CIVILIAN AND MILITARY FITNESS TRENDS

Today's youth appear less prepared for entry-level training than their predecessors given the close relationship between timed running performance and IMT aerobic fitness requirements. Pate has reported low aerobic fitness levels among one-third of American youths aged 12 through 19.[24] Other reports concerning aerobic fitness trends among American youth are conflicting, with fitness levels remaining stable or decreasing for adolescent males and females from the late 1930s onward.[5,25]

Knapik found no change in male recruits' aerobic fitness (VO_{2max}) and slightly improved female recruit fitness between 1975 and 1998.[26] In what might appear contradictory, recruits' timed running performances slowed between 1984 and 2003.[26] Similarly, running performances have slowed among males and females up to high school age across time.[26] Running performance is affected by factors other than VO_{2max}, including motivation, pacing ability, environmental issues, running economy (energy expenditure when running at a given speed), and anaerobic capacity.[24,26,27]

Few studies address muscular strength or endurance trends. The President's Council on Physical Fitness and Sports reported that American youths' upper body strength and endurance were consistently poor between 1965 and 1985.[28] Limited data indicate that male and female recruits' muscular strength increased between 1978 and 1998, whereas muscular endurance remained unchanged between 1984 and 2003.[26]

Steadily increasing failure rates on the Army's 1-1-1 physical assessment test suggest a decline in recruit fitness. The 1-1-1 test consisted of timed 1-minute push-up, 1-minute sit-up, and 1-mile run events (Table II). As per Knapik's findings and unpublished data, it appears that male recruit first-time failure rates increased from 4% in 2003 to 34% in 2009, whereas female failures increased from 10 to 47%[29] (Table III). Note that testing procedures followed through 2003 were not identical to procedures followed in subsequent years.

The Centers for Disease Control has reported increased obesity (defined as BMI > 30) among Americans across the past 2 decades.[30] Obesity prevalence among American children and adults (excluding the heaviest male youths) has apparently stabilized across the past 5 to 10 years.[31–33] Nevertheless, excessive weight/body fat remains the primary reason listed for recruit medical disqualifications, accounting for 16 to 17% of disqualifications.[3] Further, the prevalence of active duty military personnel diagnosed as being overweight or obese more than doubled from 1998 to 2008.[34]

TABLE II. U.S. Army's 1-1-1 Physical Assessment Test (Minimum Standards)[28]

Event	Male	Female
Push-Ups (Repetitions)	13	3
Sit-Ups (Repetitions)	17	17
1 Mile Run (Minutes)	8.5	10.5

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TABLE III. 1-1-1 Test Failures at Fort Jackson, South Carolina: Absolute Numbers (When Available) and Percentages by Year[28]

	January to August 1998	FY 2000	FY 2001	FY 2002	FY 2003	FY 2006[a]	FY 2009[a]	FY 2010[a]
Male	7%	4%	4%	5%	858 (4%)	3746 (22%)	3666 (37%)	5785 (40%)
Female	24%	12%	13%	15%	1580 (10%)	3734 (40%)	2587 (52%)	3269 (54%)

[a]K.W. Williams, personal communication.

CURRENT STATUS OF PHYSICAL FITNESS SCREENING

Despite the associations between physical fitness and injury risk, only the Marines and Navy screen recruits' pre-enlistment fitness levels. Marine recruits must pass a standardized Initial Strength Test (IST) administered by recruiters before proceeding to Basic Training (Table IV). Recruits must again pass the IST upon arrival at Basic Training. IST failures are assigned to a Physical Conditioning Platoon (PCP) to improve fitness before beginning Basic Training. PCP program metrics are shown in Table V. Significant variability was observed from FY 2009 to FY 2011. Although multifactorial in nature, variability may be partly due to an improved recruiting environment enabling the Marines to be more selective of applicants (B.J. McGuire, personal communication).

Beginning in 1999, the Army's Training and Doctrine Command administered the 1-1-1 test to all recruits before beginning IMT. Recruits who failed were assigned to a Fitness Training Unit (FTU), later redesignated as Fitness Assessment Program (FAP). These individuals remained within the FTU/FAP until passing the 1-1-1 test and progressing to BCT. The FAP reduced injury risk and attrition, enabling the Army to retain approximately 516 recruits and save over $14 million annually in the early 2000s.[29,35,36]

The Army eventually discontinued 1-1-1 testing and automatic assignment to the FTU/FAP (currently designated as FTU). FTU assignment is limited to recruits who repeatedly fail the Army Physical Fitness Test (APFT) despite completing all other BCT requirements. As of July 2011, approximately 93% of recruits in the FTU at Fort Jackson achieved BCT standards for the APFT (50 points per event) after performing Physical Readiness Training (PRT) for 2 to 4 weeks (M. Reed, personal communication, 2011).

Recruits assigned to the FTU perform PRT for 1.5 to 2 hours daily. Injured FTU recruits perform modified PRT and rehabilitation exercises prescribed by a physical therapist to enhance fitness while promoting soft tissue healing. Overall, FTU recruits exercise for 12 hours weekly, with 8 hours being PRT specific. In comparison, recruits in the training brigades perform PRT for not more than 1 hour daily or 6 hours weekly. When not exercising, FTU recruits perform light administrative duties or rest.

From 2005 until 2009, the Army conducted an Assessment of Recruit Motivation and Strength (ARMS). ARMS consisted of a modified Harvard step test and 1-minute push-up test. An incremental dynamic lift test was discontinued in 2006 because of high pass rates and assessment time considerations. Initially, all Army applicants underwent ARMS testing at six Military Entrance Processing stations. Attrition rates were significantly higher among those who failed ARMS testing.[4] ARMS subsequently targeted recruits who exceeded weight-for-height and body composition accession standards per anatomic circumferential measurements.[37] Recruits who passed the ARMS test received body composition enlistment waivers. They were found to be at increased risk of injury but not attrition.[38] RAND reported that the ARMS program accessed an additional 3,690 recruits in FY 2007 at an estimated per-recruit cost of $163.[39] The Army discontinued ARMS testing in September 2009 because of an improved recruiting environment.

TABLE IV. U.S. Marine Corps' IST (Minimum Standards)

Event	Male	Female
Pull Ups (Repetitions)	2	NA
Flexed-Arm Hang (Seconds)	NA	12
Crunches in 2 Minutes (Repetitions)	44	44
1.5 Mile Run (Minutes)	13.5	15.0

Physical Training, Marine Corps Recruit Depot, Parris Island. Available at http://www.mcrdpi.usmc.mil/training/physical.asp; accessed January 13, 2012.

ONGOING INJURY CONTROL INITIATIVES

The primary initiative to address training-related injuries and attrition is the PRT program.[11] PRT's inherent injury control and exercise progression components are designed to address low fitness levels across IMT. A key PRT component is decreased running frequency and duration, with greater emphasis on intensity to compensate for decreased volume. Reduced volume is based upon findings that limiting slower

TABLE V. U.S. Marine Corps' PCP Enrollment at Parris Island, South Carolina: Length of Stay and Return to Training

	FY 2009	FY 2010	FY 2011
Total Accessions	16,570 (M) 2,595 (F)	15,294 (M) 2,673 (F)	16,027 (M) 2,491 (F)
Recruits Assigned to PCP	391 (M) 255 (F)	61 (M) 103 (F)	54 (M) 54 (F)
PCP Assignments as % of Total Accessions	2.4% (M) 9.8% (F)	0.4% (M) 3.9% (F)	0.3% (M) 2.2% (F)
Average Length of Stay	59 Days (M) 42 Days (F)	17 Days (M) 20 Days (F)	23 Days (M) 25 Days (F)
Recruits Returned to Training	86% (M) 69% (F)	64% (M) 58% (F)	73% (M) 59% (F)

T.L. Bockelman, personal communication.

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recruits' mileage to approximately 25 miles across a 9 week BCT minimizes risk while sufficiently improving performance to pass the APFT.[40] Across three studies, the adjusted risk of injury was 1.5 to 1.8 times greater among Soldiers performing traditional physical training when compared with Soldiers performing PRT.[41]

The Army has instituted additional initiatives to reduce injury risk and improve performance within the IMT and operational environments. The Initial Entry Training Soldier Athlete Initiative introduces a musculoskeletal action team seeking to determine the best combination of health care and fitness professionals for injury prevention, performance optimization, and musculoskeletal rehabilitation in IMT. At the operational level, the Military Power, Performance, and Prevention (MP3) trial promotes automated technology to more efficiently perform a battery of fitness assessments (including Functional Movement Screen and Y-balance performance) on more than 1,750 Soldiers. The MP3 trial's primary purpose is to determine which functional assessments are predictive of injury risk at the operational level. Should the MP3 trial achieve this purpose, further research could evaluate whether these functional assessments are predictive of injury risk during IMT (T.L. Pendergrass and D.S. Teyhen, personal communication).

RECOMMENDED INTERVENTIONS

Disagreement exists concerning preaccession fitness screening. Describing Basic Training as an "expensive screening function," the National Research Council recommends preaccession testing for all Services.[5] In contrast, the Joint Services Physical Training Injury Prevention Work Group, chartered by the Defense Safety Oversight Council, found insufficient evidence to recommend pre-Basic Training fitness assessment and programming for the least-fit recruits.[42]

The authors recommend resuming 1-1-1 testing at recruiting stations for all recruits and ARMS testing at Military Entrance Processing stations for recruits exceeding body composition accession standards. One could defer recruits failing 1-1-1 or ARMS testing, provide training guidance, and retest in 8 to 12 weeks. A pre-IMT fitness program and standardized fitness guide address this need.[43,44]

Low-fit recruits could be placed in Delayed Entry Program-type status, with enlistment contingent upon passing the retest.[5] Eight to 12 weeks of training should suffice for fitness improvement; greatest aerobic and strength gains typically occur during the first 2 to 3 months after beginning exercise.[45,46] Requiring recruits to meet minimum pre-enlistment fitness standards could screen out individuals who fail to respond or lack the motivation to adhere to an exercise program. Screening could positively influence injury and attrition rates; physical fitness and motivation levels have been associated with attrition during IMT.[4]

The authors also recommend that recruits again undergo 1-1-1 testing upon arrival at BCT. Although this may seem redundant, the Marines' experience with recruits passing the recruiting station IST, but subsequently failing the Basic Training IST highlights the potential benefit. Recruits who fail could train per PRT principles within the FTU until passing a retest.

Delaying 1-1-1 testing until arrival at BCT and subsequent FTU assignment for low-fit recruits is a less desirable alternative to testing at both the recruiting station and BCT. This option would enable larger recruiting pools and still provide fitness programming to low-fit recruits before beginning BCT. However, the cost associated with accessing recruits who are subsequently discharged for repeated 1-1-1 test failures despite FTU assignment is a trade-off with this alternative.

The authors do not recommend resuming gender-separate physical training during BCT. The Army has maintained integrated physical training since 1995, with recruits separated into ability-based running groups. The integrated approach is supported by findings that males and females are at relatively equal risk for injury when matched for aerobic fitness.[8] Integrated training is also supported by Knapik's report in 1999 that female recruits' injury incidence relative to their male counterparts remained consistent despite switching from gender-separate to integrated training.[47]

However, gender-separate training remains an option should PRT and ability-based running groups not sufficiently address female injury and attrition rates. Athletic women may still be at slightly greater risk for stress fractures when compared with male athletes of relatively similar fitness levels.[48] Also, there are trends of increased injury risk among female recruits with lesser load carrying and dynamic lifting capabilities.[7] The National Research Council has questioned whether gender-based anatomical and physiological differences place female recruits at increased risk regardless of injury prevention and fitness-based interventions.[5]

CONCLUSIONS

Training-related injuries negatively impact the Army. Low (particularly aerobic) fitness levels among recruits are associated with increased risk for injury and attrition. PRT programming has been shown to decrease injury rates, but low-fit recruits remain at increased risk regardless of program design.

The authors recommend pre-enlistment fitness screening whenever possible. Delaying enlistment of low-fit recruits or immediately placing them in FTU-based programs until they met minimal standards would likely decrease the incidence of injuries. Further, pre-enlistment ARMS testing would enable the Army to screen in fit and motivated recruits who exceed weight-for-height and body composition accession standards.

The decision whether to screen for fitness before beginning BCT could be based upon the existing recruiting environment. The Army could screen out low-fit recruits during relatively strong recruiting periods. It could screen in fit and motivated recruits that exceed body composition accession

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standards via ARMS testing during lean recruiting periods. It could also provide FTU-based fitness programming to low-fit recruits before beginning BCT during lean recruiting periods. The Army should anticipate increased injuries and attrition when discontinuing screening and/or fitness programming for low-fit recruits.

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CONSENSUS STATEMENT

International Olympic Committee (IOC) Consensus Statement on Relative Energy Deficiency in Sport (RED-S): 2018 Update

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In 2014, the International Olympic Committee (IOC) published a consensus statement entitled "Beyond the Female Athlete Triad: Relative Energy Deficiency in Sport (RED-S)". The syndrome of RED-S refers to: "impaired physiological functioning caused by relative energy deficiency, and includes but is not limited to impairments of metabolic rate, menstrual function, bone health, immunity, protein synthesis, and cardiovascular health." The aetiological factor of this syndrome is low energy availability (LEA) (Mountjoy et al., 2014).

The publication of the RED-S consensus statement stimulated activity in the field of Female Athlete Triad science, including some initial controversy (De Souza, Williams, et al., 2014; Mountjoy, Sundgot-Borgen, Burke, Carter, Constantini, Lebrun, Meyer, Sherman, Steffen, Budgett, & Ljungqvist, 2015) followed by numerous scientific publications addressing:

1. The health parameters identified in the RED-S conceptual model (Figure 1) (Constantini, 2002; Mountjoy et al., 2014)

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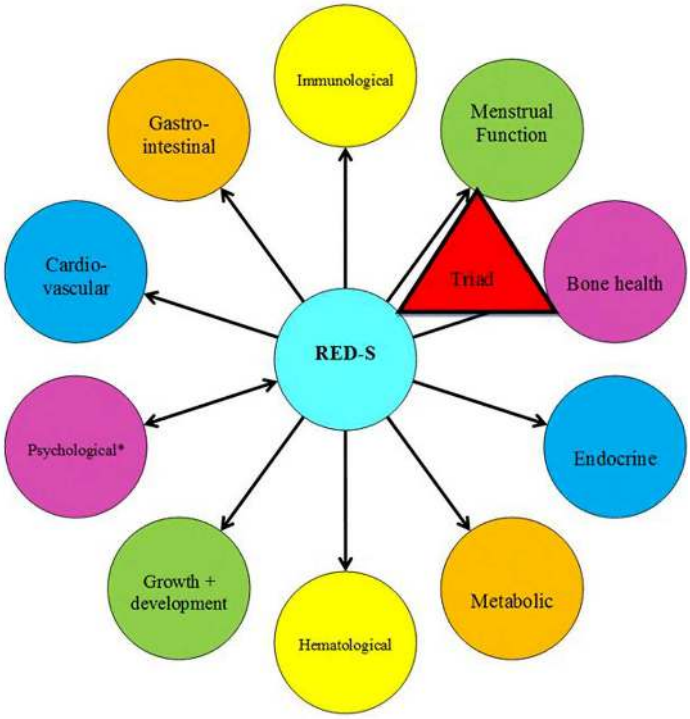

Figure 1 — Health Consequence of Relative Energy Deficiency in Sport (RED-S) showing an expanded concept of the Female Athlete Triad to acknowledge a wider range of outcomes and the application to male athletes (*Psychological consequences can either precede RED-S or be the results of RED-S).

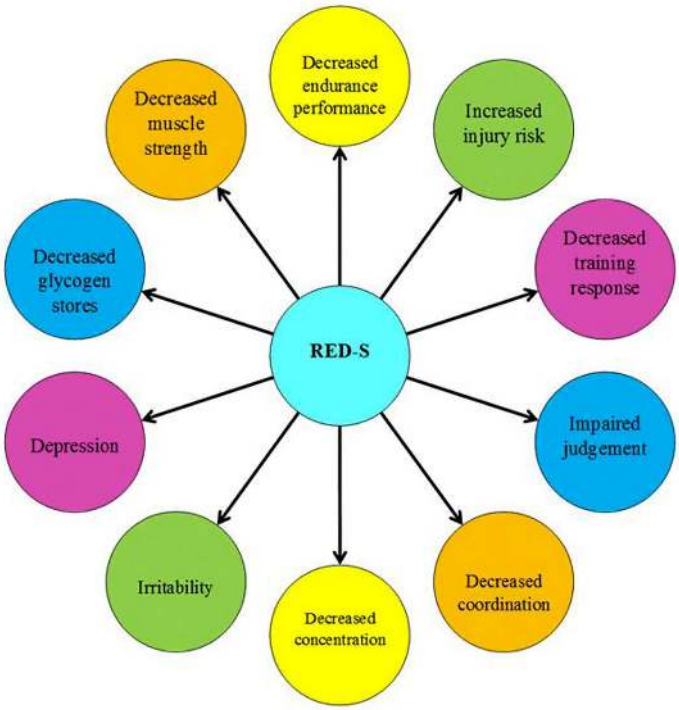

Figure 2 — Potential Performance Effects of Relative Energy Deficiency in Sport (RED-S) (*Aerobic and anaerobic performance) Adapted from Constantini.

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2. Relative energy deficiency in male athletes
3. The measurement of LEA
4. The performance parameters identified in the RED-S conceptual model (Figure 2) (Constantini, 2002; Mountjoy et al., 2014)

The IOC RED-S consensus authors have reconvened to provide an update summary of the interim scientific progress in the field of relative energy deficiency with the ultimate goal of stimulating advances in RED-S awareness, clinical application, and scientific research to address current gaps in knowledge.

Low Energy Availability

LEA, which underpins the concept of RED-S, is a mismatch between an athlete's energy intake (diet) and the energy expended in exercise, leaving inadequate energy to support the functions required by the body to maintain optimal health and performance. Operationally, energy availability (EA) is defined as:

$$\text{Energy Availability (EA)} = [\text{Energy intake (EI) (kcal)} - \text{Exercise Energy Expenditure (EEE) (kcal)}] / \text{Fat-free mass (FFM) (kg)};$$

where exercise energy expenditure is calculated as the additional energy expended above that of daily living during the exercise bout, and the overall result is expressed relative to FFM, reflecting the body's most metabolically active tissues (Loucks et al., 2011; Melin & Lundy, 2015). Rigorously controlled laboratory trials in women have shown that optimal EA for healthy physiological function is typically achieved at an EA of 45 kcal/kg FFM/day (188 kJ/kg FFM/day) (Loucks & Heath, 1994; Loucks & Thuma, 2003). Meanwhile, although some caveats are noted in relation to differential responses of various body systems (Burke & Deakin, 2015), many of these systems are substantially perturbed at an EA < 30 kcal/kg FFM/day (125 kJ/kg FFM/day), making it historically a targeted threshold for LEA. However, recent evidence suggests that this cutoff does not predict amenorrhea in all women (Lieberman et al., 2018; Williams et al., 2015). In addition, and not withstanding differences across body sizes and pubertal age, it is noted that an EA of 30 kcal/kg/FFM roughly equates to the average resting metabolic rate (RMR) (Loucks et al., 2011). Because LEA has proven robust in explaining markers of sub-optimal health and function in both laboratory (Loucks & Heath, 1994; Loucks & Thuma, 2003) and field settings (Melin et al., 2014; Vanheest et al., 2014), it seems logical that an EA assessment could serve as a diagnostic tool in the prevention or management of RED-S.

Measurement of EA

Despite the primary importance of determining whether an athlete has adequate EA, several barriers prohibit the direct measurement of EA from being a practical and reliable option. First, there is no standardised or reference protocol for undertaking an EA assessment (e.g., the number of collection days, methodologies for assessing energy intake, exercise energy expenditure, or FFM). Furthermore, there are significant concerns over the reliability and validity of each of these metrics. The greatest challenge is to gain an accurate record of usual energy intake from self-reported sources (Burke, Melin, et al., 2018; Burke & Deakin, 2015). Other

challenges include the measuring of exercise energy expenditure during many of the training/competition activities performed by athletes and accounting for their additional recreational/lifestyle activity (Burke & Deakin, 2015; Cialdella-Kam et al., 2014). These problems may partially explain why many field studies report considerable discrepancies between EA calculations and symptoms associated with LEA (Aparicio-Ugarriza et al., 2015; Burke, Melin, et al., 2018; Burke & Deakin, 2015; Levine, 2005; Pinheiro Volp et al., 2011). However, other explanations for these observations include: 1) the temporal dissociation between the period of mismatched eating and exercise behaviour that created the LEA problems and the occasion on which the EA assessment was undertaken; and 2) the interaction of other dietary characteristics that often co-exist with LEA and may exacerbate its effects (e.g., high intake of fibre, stimulants and artificial sweeteners; low energy density foods; high dietary restraint, poor spread of energy within a day) (Barron et al., 2016; Gaskins et al., 2009; Heikura et al., 2017; Melin et al., 2016; Reed et al., 2014). Even if these problems could be solved, EA calculations would likely involve specialised equipment and expertise (e.g., dual energy x-ray absorptiometry (DXA) measurement of body composition), good motivation and compliance of the athlete (e.g., keeping a food record or comprehensive activity diary), and considerable time and expertise to process the information. Additionally, LEA states may develop at different stages of training and competition due to varying physiological demands. An EA assessment may achieve some valuable outcomes, such as strengthening the interaction between the practitioner and athlete, which can create rapport, trust, and an appreciation of EA needs. However, the considerable effort needed to assess EA and its frailties as a stand-alone diagnostic tool prevent expert bodies from instituting it as a universally recommended measurement.

Low Energy Availability in Male Athletes

Similar to female athletes, there is growing evidence that males may experience LEA in situations when there is a mismatch between energy intake and the exercise energy expenditure of training or competition. Populations of male athletes at increased risk for LEA and resulting health consequences of RED-S include cyclists, rowers, runners, jockeys, and athletes in weight class combat sports (Barrack et al., 2017; Berkovich et al., 2016; Burke, Tenforde, et al., 2018; Fagerberg, 2017; Tenforde et al., 2016; Viner et al., 2015; Wilson et al., 2014). Factors that contribute to LEA in male athletes are varied and often unique to the sport. They include the cyclical changes in body mass and composition ("making weight"), prolonged inadequate energy intake to meet high exercise energy expenditure of endurance sport, punctuated changes in training volume/intensity, and participation in strenuous endurance events without accompanied changes in nutrition (Burke, Tenforde, et al., 2018). Inadequate food availability, including food insecurity from cultural practices or lack of financial resources may also contribute risk for LEA in some male athletes, even among high calibre athletes, as it undoubtedly also does in female athletes (Burke, Tenforde, et al., 2018).

While RED-S may occur in both sexes, there are likely differences in biological responses to LEA in male athletes compared to their female counterparts. The prevalence of LEA has been suggested to be higher in females than in males, although precise differences are unknown (Loucks, 2007). The threshold and duration of the LEA state required to induce RED-S in men is unknown. Reduction in the sex hormone testosterone is likely to be of greater health concern in male athletes (Hackney et al., 2005; Hooper et al., 2017; Tenforde et al., 2016).

Low Energy Availability in Para Athletes

The prevalence of LEA in para athletes is incompletely characterized (Blauwet et al., 2017). When extrapolating from trends noted in general populations of individuals with disability, it can be assumed that athletes who use a wheelchair for daily mobility are likely to have reduced baseline energy needs (Buchholz & Pencharz, 2004; Price, 2010). Despite this, male and female athletes with spinal cord injury (SCI) may monitor or restrict body weight for sport and are at risk for nutrient deficiencies (Krempien & Barr, 2011, 2012). Athletes with central neurologic injury, such as cerebral palsy, who demonstrate aberrant movement patterns that include dyskinesis or athetosis, may have higher energy expenditures than similar athletes without such non-purposeful movements (Crosland & Boyd, 2014). Additionally, the presence of central neurologic injury may result in alterations of the hypothalamic-pituitary axis and baseline menstrual function, regardless of energy status (Colantonio et al., 2010; Ranganathan et al., 2016; Ripley et al., 2008). Amputee athletes may have higher energy needs in the setting of prosthetic use and resultant gait asymmetry (Gonzalez et al., 1974).

Para athletes are at high risk for impaired bone health and bone-related injury secondary to many factors, including altered skeletal loading. For example, in unilateral amputees, the affected limb may exhibit reduced bone mineral density (BMD) (Sherk et al., 2008). Athletes with SCI have disuse osteopenia/osteoporosis affecting the lower extremities, however, positive adaptive changes in upper body BMD values have been reported in wheelchair basketball players compared to non-athletes (greater radial BMD, and trend towards increased lumbar BMD) (Goktepe et al., 2004). Characterizing effects of LEA on bone in para athletes requires consideration of baseline effects of each individual's underlying disability. More work is needed in this area.

Given rising participation in para sport from grassroots to elite levels, further research is needed to investigate the impact of LEA in athletes with a disability. The para athlete population requires screening for LEA to reduce complications of RED-S, including low BMD.

Race and Low Energy Availability

Whether race plays a role in the incidence and underlying aetiology of RED-S remains speculative. Research shows a lower risk of disordered eating (DE) in African-American, but not Latino female high-school athletes compared to Caucasians (Pernick et al., 2006; Rhea, 1999). It is currently unknown whether the prevalence of menstrual disorders differs among racially diverse athletic groups. Stress fractures in African-American military recruits are lower than in Caucasian recruits (Lappe et al., 2001). Meanwhile, male Kenyan runners have been observed to have greater BMD at weight-bearing sites (e.g., proximal femur) than healthy controls, but not at the lumbar spine, where Z-scores were reported to be below -2.0 in 40% of study subjects (Tam et al., 2018). Such runners may have LEA resulting from low energy intake and high exercise energy expenditure associated with heavy training loads (Tam et al., 2018), as has been previously shown (Mukeshi & Thairu, 1993; Onywera et al., 2004). In another study of young Kenyan female athletes, middle- and long-distance runners were found to exhibit one or more subclinical and/or clinical components

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of the RED-S, including a greater risk for LEA and menstrual dysfunction than controls (Muia et al., 2016). A study of sport nutrition knowledge, behaviors, and beliefs across sex, race/ethnicity, and socioeconomic status in high school soccer players identified that general sports nutrition knowledge is lower in adolescent soccer players compared to prior reports in adolescent athletes, and that specifically females and Latinos may benefit from sport nutrition education (Manore et al., 2017). Published research is greatly lacking on RED-S in African American, Hispanic, and Asian athletes, with a few exceptions (Iwamoto et al., 2011; Quah et al., 2009). Thus, there is a need to include more diverse athlete populations in RED-S research and to integrate race/ethnicity in the prevention and treatment of RED-S.

Health Effects of Low Energy Availability

Endocrine

Effects of LEA on the endocrine system have been described predominantly in female athletes and only recently in male athletes. Findings in some female athletes in LEA states (measured EA and/or athletes with amenorrhea) include disruption of the hypothalamic-pituitary-gonadal axis, alterations in thyroid function, changes in appetite-regulating hormones (e.g., decreased leptin and oxytocin, increased ghrelin, peptide YY, and adiponectin), decreases in insulin and insulin-like growth factor 1 (IGF-1), increased growth hormone (GH) resistance, and elevations in cortisol (Allaway et al., 2016; Ihle & Loucks, 2004; Logue et al., 2018; Loucks & Thuma, 2003; Misra, 2014). Many of these hormonal changes likely occur to conserve energy for more important bodily functions or to use the body's energy reserves for vital processes (Jasienska, 2003; Wade & Jones, 2004).

Specific changes in men are not completely understood; however, reduced LH pulsatility and amplitude have been described in a case series of male marathon runners, a population at high risk for LEA (MacConnie et al., 1986). Other studies, primarily in endurance male athlete populations, have shown reductions in testosterone and inconsistent findings in differences in basal LH parameters (Hackney et al., 1988; McColl et al., 1989). Koehler et al. (2016) assessed the effects of short-term EA manipulation through diet and exercise on various hormonal parameters in 6 male habitual exercisers. Each male experienced 4 separate 4-day conditions: LEA (15 kcal/kg FFM/day with and without exercise) and adequate EA (40 kcal/kg FFM/day with and without exercise). Following both LEA conditions, regardless of exercise, leptin and insulin were reduced compared to baseline (–53% to –56% and –34% to –38%, respectively). LEA did not significantly affect ghrelin, triiodothyronine (T_3), testosterone, or IGF-1 levels. Thus, the LEA state, often in combination with disruptions to endocrine function in women and possibly men, may contribute to multiple physiological disease states described by RED-S. However, the relationship is likely to be subject to a large degree of within- and between-participant variability; more research is needed, particularly in men (Papageorgiou, Dolan, et al., 2018; Papageorgiou, Elliott-Sale, et al., 2017; Williams et al., 2015).

Menstrual Function

The effects of LEA on reproductive hormones and menstrual function in female athletes have been well-described (Gordon et al., 2017; Loucks & Thuma, 2003; Nattiv et al., 2007), although the complex hormonal signaling pathways underpinning these effects are still being fully elucidated. Current evidence supports a LEA-associated disruption of Gonadotropin Releasing Hormone (GnRH) pulsatility at the hypothalamus, followed by alterations of LH and FSH release from the pituitary and decreased estradiol and progesterone levels; this is considered a form of functional hypothalamic amenorrhea (FHA) (Curry et al., 2015; Gordon et al., 2017). The duration and severity of LEA needed to create such disturbances are also unclear, reflecting both the complex nature of the problem and discrepancies associated with the different methodologies used to study it. For example, Loucks and Thuma (2003) studied previously sedentary women in a laboratory setting and identified that well-controlled interventions reducing EA below 30 kcal/kg FFM/day via the short-term (5 day) manipulation of exercise energy expenditure and energy intake were associated with a dose-response decrease in LH pulsatility. More recently, Williams, et al. (2015) reduced EA via manipulation of energy intake and exercise energy expenditure over several menstrual cycles in untrained, previously eumenorrheic subjects. The researchers found that the frequency of menstrual disturbances (including luteal phase defects, anovulation, and oligomenorrhea) was affected by the magnitude of energy deficit compared to baseline needs (Williams et al., 2015), but a specific threshold of EA below which menstrual disturbances occurred was not identified (Lieberman et al., 2018).

Meanwhile, Reed et al. (2015) performed a cross-sectional analysis of EA (measured using 3-day diet logs to determine energy intake and a combination of exercise logs and heart rate monitoring to measure estimated exercise energy expenditure) in female athletes with eumenorrhea and various menstrual disturbances. These investigators reported mean EA was >30.0 kcal/kg FFM/day in all the groups (amenorrheic, oligomenorrheic, ovulatory eumenorrheic, inconsistent subclinical menstrual dysfunction eumenorrheic, and anovulatory eumenorrheic athletes) and EA did not discriminate subclinical forms of menstrual disturbance; however, EA was lower in amenorrheic athletes compared to eumenorrheic athletes (mean 30.9 vs. 36.9 kcal/kg FFM/day) (Reed et al., 2015). Thus, severe energy deficiency is known to lead to amenorrhea, but more work is needed to better understand the interplay of change in short and long-term EA and more subtle menstrual disruption.

Bone Health

It is established that LEA contributes to impaired bone health in athletes, particularly women. Cross-sectional studies of physically active female athletes with oligo-/amenorrhea or measured LEA have demonstrated decreased BMD, altered bone microarchitecture and bone turnover markers, decreased estimates of bone strength, and increased risk for bone stress injuries compared to eumenorrheic athletes and those who are energy replete (Ackerman et al., 2011, 2012; De Souza et al., 2008; Nattiv et al., 2007; Papageorgiou, Dolan, et al., 2018). Short-term LEA (via diet and exercise) has prospectively been shown to negatively affect bone turnover markers in women and some men (Ihle & Loucks, 2004; Papageorgiou, Elliott-Sale, et al., 2017). Specific female and male sport populations are at increased risk for lower BMD, including jockeys, runners, swimmers, and cyclists (Andreoli & Monteleone, 2001; Barrack et al., 2008, 2017; Fredericson et al., 2007; Hind et al., 2006; Morel et al., 2001; Nichols & Rauh, 2011; Stewart & Hannan, 2000; Tenforde et al., 2015; Viner et al., 2015; Wilson et al., 2014, 2015). Anatomical sites with less bone loading and/or greater trabecular versus cortical bone content (lumbar spine and

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radius vs. total hip) are at greater risk for low BMD and impaired microarchitecture in populations susceptible to LEA (Ackerman et al., 2011, 2012; Bilanin et al., 1989; Fredericson et al., 2007; Hind et al., 2006).

Low body mass index (BMI) is an imperfect surrogate marker for LEA. However, BMI ≤ 17.5 kg/m^2, <85% expected body weight for adolescents or ≥ 10% weight loss in one month are proposed indicators of LEA (De Souza, Nattiv, et al., 2014), and indeed both BMI and expected body weight cutoffs are associated with increased risk for low BMD in both sexes (Barrack et al., 2017; Tenforde et al., 2015; Thralls et al., 2016). LEA may be accompanied by DE/eating disorders (EDs), menstrual dysfunction, and low BMD, and the combination of factors places athletes at higher risk for bone stress injury (Ackerman et al., 2015; Barrack et al., 2014; Tenforde et al., 2017).

Metabolic

LEA has been correlated with decreased RMR in female endurance athletes (Melin et al., 2015). Prospectively, increasing training load while maintaining constant EI over 4 weeks in male and female elite rowers led to a significant reduction in RMR (Woods et al., 2017). In normal weight women with induced energy deficits via exercise and dietary manipulation, measured weight loss over 3 months was less than predicted (Koehler et al., 2017). Subjects who were moderately energy deficient had a significant decrease in RMR, and those who were severely energy deficient demonstrated significant decreases in leptin, T_3, IGF-1, and an increase in ghrelin (Koehler et al., 2017).

Hematological

Iron is essential for hematopoiesis and subsequent oxygen carrying capacity. Iron deficiency, often seen in female athletes, can contribute directly and indirectly to energy deficiency. This is due to a potential reduction in appetite, decreased metabolic fuel availability, and impaired metabolic efficiency, leading to an increase in energy expenditure during exercise and rest (Petkus et al., 2017). Iron deficiency may also interact with bone health via dysregulation of the GH/IGF-1 axis, hypoxia, and hypothyroidism, in addition to playing an important role in thyroid function, fertility, and even psychological well-being (Petkus et al., 2017). Thus, LEA may be partially induced by, and may contribute to, iron deficiency (Petkus et al., 2017). Surrogates for LEA have been correlated with hematologic dysfunction, including low ferritin and iron deficiency anemia, in adolescent and young adult female athletes (Ackerman et al., 2018).

Growth and Development

Linear growth retardation has been reported in various studies of male and female adolescents with severe anorexia nervosa, with studies demonstrating partial, but not always complete, catch-up growth after recovery (Lantzouni et al., 2002; Modan-Moses et al., 2003, 2012). Decreases in IGF-1, increases in GH, and increased GH resistance are consistently noted in those with anorexia nervosa (Fazeli & Klibanski, 2014). Studies in amenorrheic athletes have demonstrated disorderly GH secretory patterns, decreased GH and IGF-1 secretory response to exercise accompanied by increased interpulse GH levels, and decreased IGF-1/IGFBP-1 ratios, with more research needed to understand training and growth implications (Laughlin & Yen, 1996; Waters et al., 2001).

Cardiovascular. Early atherosclerosis may be associated with hypoestrogenism and FHA in young athletes (O'Donnell et al., 2011). Endothelial dysfunction and unfavorable lipid profiles have been reported in amenorrheic athletes (Rickenlund et al., 2005), with resumption of menses leading to improvements in vascular endothelial function (Hoch et al., 2007). In one study, amenorrheic athletes demonstrated lower heart rates and systolic blood pressure compared to eumenorrheic athletes, in addition to disruptions of the normal renin-angiotensin-aldosterone response to an orthostatic challenge (O'Donnell et al., 2015). In the more severe LEA state of anorexia nervosa, significant cardiovascular changes can occur, including valve abnormalities, pericardial effusion, severe bradycardia, hypotension, and arrhythmias (Spaulding-Barclay et al., 2016).

Gastrointestinal. In the severe LEA state of AN, negative health influences on the full gastrointestinal tract such as altered sphincter function, delayed gastric emptying, constipation, and increased intestinal transit time, have been described (Norris et al., 2016). Melin et al. (2014) measured EA and developed the Low Energy Availability among Female Athletes Questionnaire (LEAF-Q), both of which found a negative correlation with EA and gastrointestinal symptoms in elite Swedish and Danish athletes. These findings were supported in a survey of adolescent American female athletes with surrogate markers of LEA, who also reported a higher incidence of stool leakage and constipation than those considered to have adequate EA (Ackerman et al., 2018).

Immunological. The immune system may be altered by LEA. A study of 21 Japanese elite, collegiate runners reported more upper respiratory symptoms and lower immunoglobulin A secretion rates in the amenorrheic versus eumenorrheic athletes (Shimizu et al., 2012). Meanwhile, in observational studies of elite Australian athletes in preparation for the 2016 Rio Olympic Games, LEA, as measured by the LEAF-Q in female athletes, was associated with increased likelihood of illnesses (including those of the upper respiratory tract and gastrointestinal tract), bodily aches, and head-related symptoms in the previous month (Drew et al., 2017, 2018).

Psychological. Psychological problems can precede or be caused by LEA (Mountjoy et al., 2014). LEA in athletes has been shown to have negative correlates with various aspects of psychological well-being. Higher drive for thinness may be a proxy for LEA, as higher drive for thinness scores on the Eating Disorder Inventory have been associated with reduced resting energy expenditure, lower T_3 levels, and higher ghrelin levels in female athletes (De Souza et al., 2007). Athletes who scored higher on DT also scored higher in domains of ineffectiveness, cognitive restraint, and bulimic tendencies (De Souza et al., 2007). Adolescent females with FHA have been found to have a higher incidence of mild depressive traits, psychosomatic disorders, and a decreased ability to manage stress (Bomba et al., 2007; Marcus et al., 2001). A separate study found overlap in adolescents with anorexia nervosa and those with FHA: both groups demonstrated increased depression, social insecurity and introversion, and fears of weight gain compared to healthy controls (Bomba et al., 2014). More profound psychological disturbances were seen in the presumably more restricted EA (anorexia nervosa) group versus the FHA group (Bomba et al., 2014). Results from a study with male athletes indicated that dietary restraint and muscle building behaviors were associated with bulimic symptomatology (Petrie et al., 2014). Additionally, studies of male body builders indicate that a prolonged EA of approximately 20–25 kcal/kg FFM/day, as seen in

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the final stage of contest diets, might be pathological and have negative psychological effects for males (Fagerberg, 2017). The restrictive diet patterns observed resulted in a reduction in muscle mass and a loss of strength, with reports of endocrine dysfunction and mood disturbances in those athletes with body composition measurements of approximately 4% total body fat (Fagerberg, 2017).

Disordered Eating and Eating Disorders

Disordered eating and eating disorders are more prevalent among female and male athletes in weight-sensitive sports in comparison to athletes representing sports in which leanness is a less important performance variable (Kong & Harris, 2015; Sundgot-Borgen, 1993; Sundgot-Borgen & Torstveit, 2004; Sykora et al., 1993; Thiemann et al., 2015). In a Norwegian study of adolescent elite male and female athletes, a higher prevalence of disordered eating in non-athletes as compared to athletes was found when using questionnaires (Martinsen et al., 2010), but when using a clinical interview, the prevalence of eating disorders was higher in athletes versus controls (Martinsen & Sundgot-Borgen, 2013). These findings suggest the need for personal interviews to diagnose eating disorders in athletes (Fairburn et al., 2008; Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004). It should be noted that the revised diagnostic criteria for eating disorders (Diagnostic and Statistical Manual, 5th edition) may influence the prevalence of the different diagnoses among athletes (American Psychiatric Association, 2013; Vo et al., 2017).

The pathogenesis of eating disorders is multifactorial with cultural, familial, individual, and genetic/biochemical factors playing roles (Stice et al., 2012). Weight pressure and unique eating disorder risk and trigger factors have been reported and include performance pressure, sudden increase in training volume, injury, teammate modeling of eating disorder behaviors, and team weighins (Arthur-Cameselle et al., 2017; Krentz & Warschburger, 2013; Sundgot-Borgen, 1994). A desire to be leaner to enhance performance seems to predict later disordered eating (Krentz & Warschburger, 2013), and the risk of eating pathology increases when the coach-athlete relationship is characterized by high conflict and low support (Shanmugam et al., 2014). Disordered eating seems to be influenced by perfectionism, competitiveness, pain tolerance, and the perceived performance advantage of weight loss (Stirling & Kerr, 2012). These suggested risk factors need to be validated to demonstrate a causal relationship. However, these findings serve as a call to action for enhanced screening for eating disorder risk among athletes who experience weight pressure, are injured, or who have teammates with known disordered eating/eating disorders (Arthur-Cameselle et al., 2017).

Performance Consequences of Low Energy Availability

Associations between various surrogates of LEA (e.g., hormonal aberrations, oligo-/amenorrhea, leanness sport participation, and increased scores on ED/DE/LEA screening tools) and factors negatively influencing performance (e.g., illness, injury, iron deficiency, impaired cognition and mood) have been reported (Ackerman et al., 2015, 2018; Baskaran et al., 2017; Burden et al., 2015; Geesmann et al., 2017; Hagmar et al., 2013; Harber et al., 1998; Petkus et al., 2017; Rauh et al., 2010; Thein-Nissenbaum et al., 2014). Intervention studies on long-term energy restriction and sport performance are lacking (El Ghoch et al., 2013). However, it has been postulated that persistent LEA could impair sport performance through a variety of different indirect mechanisms (e.g., impaired recovery leading to premature reduction in physical, psychological, and mental capacity and impairment of optimal muscle mass and function) (Fogelholm, 1994). Indeed, LEA could be expected to impair performance or interfere with optimal performance gains via acute impairment of key processes such as glycogen storage (Tarnopolsky et al., 2001) or protein synthesis (Areta et al., 2014), or by preventing consistent and high quality training due to the increased risk of injury and illness (Drew et al., 2017, 2018).

Despite the importance of these associations, it is only recently that studies have tried to measure the direct impact of LEA on sports performance. For example, Silva and Paiva (2016) reported that athletic performance, measured as competition ranking, negatively correlated with EA in elite rhythmic gymnasts. Furthermore, Tornberg et al. (2017) found no difference in aerobic capacity [VO_2, O_2 (mL/min/kg)] between elite eumenorrheic endurance athletes and elite endurance athletes with secondary FHA, despite lower body weight and fat mass in the athletes with FHA. However, subjects with FHA had decreased neuromuscular performance (measured as knee muscular strength and endurance) and reaction time compared with the eumenorrheic athletes (Tornberg et al., 2017). Overall, lower neuromuscular performance was associated with higher cortisol levels, and lower blood glucose, T_3, estrogen, and FFM in the tested leg (Tornberg et al., 2017). Although striving for a greater power to mass ratio is commonly regarded as important for running performance, this study suggests that achieving an idealized body weight or body composition through severe and persistent energy restriction is likely to negatively affect performance and health (Tornberg et al., 2017). This finding is supported in a study of East African runners (Mooses & Hackney, 2017). Woods et al. (2017) followed male and female national team rowers through a 4 week intensified training period, which was accompanied by a lack of increase in energy intake despite a 21% increase in training load. It was concluded that inadequate EA likely negatively affected training recovery, at least partially explaining the alterations in 5 km time trial pacing strategy and reduced performance (Woods et al., 2017).

Considering the reported high prevalence of menstrual dysfunction caused by energy deficiency (Gibbs et al., 2013), surprisingly, only one study has investigated the direct impact of LEA on sport performance. Vanheest et al. (2014) reported a 10% decline in swimming velocity over a 400 m time trial (after 12 weeks of training) among young elite swimmers with ovarian suppression secondary to energy deficiency compared to an 8% improvement in their eumenorrheic teammates. Clearly, more investigations, including robust protocols involving random allocation of athletes to intervention groups, are needed to provide further evidence and explanation of the effects of LEA on training adaptations and sport performance.

Prevention of Relative Energy Deficiency in Sport

The prevention of RED-S requires increased awareness among athletes and their entourage. Current evidence suggests that there is much work to be done. Surveys have reported that less than 50% of physicians, coaches, physiotherapists and athletic trainers could identify the Triad components (LEA with or without an eating disorder, menstrual dysfunction, and low BMD) (Brown et al.,

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2014; Curry et al., 2015; Feldmann et al., 2011; Kroshus et al., 2014; Mukherjee et al., 2016; Pantano, 2006, 2017; Troy et al., 2006), and only 19% of 370 U.S. high school nurses could identify all three Triad components (Kroshus et al., 2015). In a survey of 931 multi-specialty physicians, only 37% were aware of the Triad, and only one half of these were comfortable treating or referring a patient (Curry et al., 2015). In a group of exercising Australian women, one third believed irregular periods were "normal" for active females, and approximately half reported knowing that menstrual dysfunction was a risk factor for poor bone health (Miller et al., 2012). Educational programs typically identify their target audiences as health professionals, coaches, athletic trainers, teachers, school administrators, athletes, and parents (Torres-McGehee et al., 2012). However, a survey of International Sport Federations (IFs) identified that only 2 of 28 Olympic IFs had programmes on RED-S, indicating the need to also involve a top-down approach (Mountjoy et al., 2018). Peer-based eating disorder/body image/Triad education and cognitive-dissonance based programs have shown promise (Brown et al., 2016; Kilpela et al., 2016; Temme et al., 2013; Valliant et al., 2012), and similar RED-S peer-led programs should be developed.

Effective eating disorder prevention programs should be multi-modal, interactive, and target athletes and coaching staff (Bar et al., 2016). One successful intervention is a peer-led educational program for female athletes that resulted in improved bulimic pathology one-year post intervention (Becker et al., 2012). A Norwegian school-based controlled intervention program, including elite male and female athletes (Martinsen et al., 2014) and coaches (Martinsen et al., 2015), resulted in no new cases of eating disorders among females in the intervention schools as opposed to 8 (13%) in females at the control schools (Martinsen et al., 2014). There was only one new eating disorder case in a male at a control school and none in males from the intervention schools (Martinsen et al., 2014). These results suggest that effective disordered eating and eating disorder prevention should target individuals beyond athletes and coaches, be gender specific, involve significant others, and include changes to sport regulations, policy measures. and the health care system (de Bruin, 2017).

Screening for Relative Energy Deficiency in Sport

Early detection of athletes at risk for energy deficiency is critical to prevent long-term health sequelae (De Souza, Nattiv, et al., 2014; Mountjoy et al., 2014; Nattiv et al., 2007). There are several disordered eating/eating disorder screening tools intended for general population (Fairburn & Beglin, 1994; Garner et al., 1983; Garner & Garfinkel, 1979; Hill et al., 2010). Some tools have been developed to target athletes, although none are validated for DSM-5 criteria (Hinton & Kubas, 2005; McNulty et al., 2001; Steiner et al., 2003). Additionally, due to stigma associated with eating disorders, athletes may be motivated to hide their illness. An elevated Eating Disorder Inventory – drive for thinness score (Garner et al., 1983) has been reported to indicate energy deficiency in exercising women (Gibbs et al., 2011), and amenorrheic athletes seem more likely to have an elevated drive for thinness score compared to eumenorrheic athletes (Gibbs et al., 2011). In order to diagnose an eating disorder, additional in-depth personal interviews must be performed (Fairburn et al., 2008; Fairburn & Beglin, 1994; Martinsen & Sundgot-Borgen, 2013; Sundgot-Borgen & Torstveit, 2004). However, the prevalence of energy deficiency is reported to be high in some athletes even without the presence of disordered eating/eating disorders (Gibbs et al., 2013; Melin et al., 2015).

Although coaches are in an ideal situation to identify athletes with disordered eating/eating disorders, they sometimes have difficulty distinguishing between athletes whose appearance or body composition metrics meets their sport-type expectations (e.g., thin) from those with an eating disorder, especially if the athlete's performance is good (Plateau et al., 2013). Even if disordered eating is identified, coaches may have difficulty convincing athletes to seek treatment (Plateau et al., 2017).

The Periodic Health Examination (Ljungqvist et al., 2009) and the Preparticipation Physical Evaluation (American Academy of Family Physicians et al., 2010) include relevant questions that may be helpful for early detection. Recently, the LEAF-Q was developed (Melin et al., 2014) as a brief questionnaire on physiological symptoms linked to energy deficiency, and the Low Energy Availability in Males Questionnaire (LEAM-Q) is in development. Expanded testing of these questionnaires in various athletic populations is needed. There is limited evidence for the efficacy of self-reported questionnaires, and additional individual evaluation is recommended (De Souza, Nattiv, et al., 2014; Mountjoy et al., 2014). The RED-S Clinical Assessment Tool (RED-S CAT) can assist clinicians in screening for RED-S and the management of return to play decisions (Mountjoy, Sundgot-Borgen, Burke, Carter, Constantini, Lebrun, Meyer, Sherman, Steffen, Budgett, Ljungqvist, et al., 2015), although validation is needed.

Treatment of Relative Energy Deficiency in Sport

Non-pharmacologic Management

If LEA is due to unintentional undereating, then simple nutritional education may suffice. Regardless of the severity of the eating pathology, early involvement of an accredited or appropriately trained expert (e.g., sports dietitian) is recommended to enhance the athlete's nutritional practices. Optimizing EA can improve function of the hypothalamic-pituitary-gonadal axis, as well as other systems negatively affected by LEA in females (Cialdella-Kam et al., 2014; Dueck et al., 1996; Kopp-Woodroffe et al., 1999; Mallinson et al., 2013). Energy deficits should be addressed via modification of exercise and nutrition practices in both female and male athletes, and energy needs may be even higher in growing adolescents (Bhasin et al., 2010; Gordon et al., 2017). Treatment is typically based on increased food intake but may also require changes in food choices, energy spread, and other dietary characteristics; these changes must be individualized and periodized according to the athlete's energy expenditure and exercise goals. A reduction or cessation of exercise may be necessary, depending on the severity of the energy deficit, symptoms, and compliance level.

Adequate bone-building nutrients are critical; for example, serum 25-hydroxy vitamin D levels <30 ng/mL are associated with increased incidence of bone stress injury (Moreira & Bilezikian, 2017; Ruohola et al., 2006). Vitamin D intake of 600-800 IU daily is recommended by USDA dietary guidelines (U.S. Department of Agriculture, 2011), but greater intake may be needed temporarily to reach goal serum 25-hydroxy vitamin D levels of >30 ng/mL (Golden & Carey, 2016; Holick et al., 2011; Sacheck et al., 2017). Improving 25-hydroxy vitamin D levels may also reduce healing time and facilitate earlier return to play for bone stress injury (Kim et al., 2016). Additionally, adequate consumption of calcium may

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help decrease the incidence of bone stress injury (Myburgh et al., 1990; Nieves et al., 2010). The current recommendation for daily calcium intake is 1000 mg/day of calcium for men and women ages 19–50 years, and 1300 mg/day for children and adolescents ages 9–18 years (US Department of Health and Human Services, 2015).

Cognitive behavioral therapy is another non-pharmacological treatment for RED-S that has been shown to contribute to the resumption of menses in some women with FHA (Berga & Loucks, 2006; Michopoulos et al., 2013). Initial non-pharmacologic management of RED-S may restore menstrual function over months (Arends et al., 2012; Mallinson et al., 2013) while improvements in bone health take longer and may never reach optimal levels (Cialdella-Kam et al., 2014). Non-compliance with therapy may require removal of the athlete from training/competition. Examples of treatment contracts and clearance categories for return to play can be found in other publications (De Souza, Nattiv, et al., 2014; Joy et al., 2016; Mountjoy et al., 2014). Current recommendations need further validation and may lead to the eventual inclusion of other progress parameters, such as RMR and blood biomarkers.

Pharmacologic Interventions

The use of combined oral contraceptives for the intention of regaining menses or improving BMD in those with RED-S is not recommended. Data regarding the effects of combined oral contraceptives on BMD and fracture risk are inconsistent (Cobb et al., 2007; Ducher et al., 2011; Gordon et al., 2017; Lopez et al., 2014, 2015). If using combined oral contraceptives for contraception, the athlete should understand that combined oral contraceptives may mask the return of spontaneous menses and bone loss may continue if the energy deficit is not corrected. If menstrual cycles do not return after a reasonable trial of nutritional, psychological and/or modified exercise interventions, transdermal estradiol (E2) therapy with cyclic oral progestin can be considered for short-term use (Gordon et al., 2017). Notably transdermal E2 is not a reliable form of hormonal contraception and an athlete should be counseled to avoid unintended pregnancy if she receives transdermal E2 for bone health. Transdermal estrogen does not affect IGF-1 secretion, a bone-trophic hormone that combined oral contraceptives downregulate, and has been shown to improve BMD in anorexia nervosa (Misra et al., 2011) and BMD and bone microarchitecture in oligo-amenorrheic athletes (Ackerman et al., 2017). Recombinant parathyroid hormone 1-34 (rPTH) has been shown to improve BMD in AN (Fazeli et al., 2014) and rare, short-term use may be considered in adults with LEA, FHA, or RED-S in the setting of delayed fracture healing or very low BMD (Gordon et al., 2017). Transdermal estrogen or rPTH should only be prescribed in conjunction with a metabolic bone expert and it is important to note that rPTH is contraindicated in adolescents and young adults with open growth plates (Gordon et al., 2017).

Treatment Strategies for Disordered Eating/Eating Disorders

Apparent disordered eating/eating disorders should be treated with a multidisciplinary team including medical, dietary, and mental health support. Inpatient treatment should be considered for patients with severe bradycardia, hypotension, orthostasis, and/or electrolyte imbalance (De Souza, Nattiv, et al., 2014; Joy et al., 2016; Temme & Hoch, 2013). Athletes' resistance to treatment usually increases with the severity of the problem (Thompson & Sherman, 2011). Because many patients with eating disorders see their disorders as purposeful and necessary (Clausen et al., 2013), motivation to recover is a critical factor in treatment. With sport participation as leverage for athletes, the desire to be healthy enough to return to sport most often facilitates recovery for athletes with eating disorders (Arthur-Cameselle & Quatromoni, 2014).

As higher levels of depression and anxiety are observed in athletes with eating pathology (Giel et al., 2016), there is a need to treat these pathologies in athletes with disordered eating/eating disorders. Additionally, comorbid disorders of depression, anxiety, and substance abuse complicate eating disorder treatment and require treatment modifications (de Bruin, 2017; Sansone & Sansone, 2007). Ideally, treatment should be provided by a mental health professional experienced in treating eating problems in athletes (Thompson & Sherman, 2011). For athletes meeting the diagnostic criteria for severe eating disorders (e.g., anorexia nervosa and bulimia nervosa), participation in competition is not recommended (Mountjoy et al., 2014).

Conclusions

Since the original publication of the IOC consensus statement on RED-S in 2014, there have been many scientific advances to improve our understanding of the health and performance effects of LEA in both female and male athletes. To address remaining gaps, the IOC RED-S consensus authors encourage scientific activity in the following domains:

1. *Identification of athletes at risk for RED-S:* It is evident that there is no practical tool for the measurement of EA, therefore, there is a recognized need to develop a methodology to screen and identify athletes at risk for RED-S that is both scientifically validated as well as relevant and applicable in clinical sport practice.
2. *Prevention of RED*-S: Improved awareness of RED-S is required through educational initiatives for athletes, coaches, members of the entourage, and sport organizations. The development of scientifically validated prevention interventions is encouraged.
3. *Male athletes:* Despite the improvement in the knowledge base of RED-S in male athletes, there remains a gap in our understanding of RED-S in specific sports with differing energy demands, performance criteria, ethnicities and cultural perspectives.
4. *Health and performance consequences of RED-S:* There is still much to be learned about the psychological and physiological health risks and long-term consequences of RED-S in all athletes, particularly male athletes, para athletes, and athletes of various races. To best engage the attention of athletes and coaches, it is imperative to further increase our understanding of the performance effects of RED-S.
5. *Treatment and 'return to play':* Practical guidelines for the treatment and safe return to play for athletes with RED-S need to be further developed to improve athletes' health and performance.

Note

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National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses

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Objective: To present best-practice recommendations for the prevention, recognition, and treatment of exertional heat illnesses (EHIs) and to describe the relevant physiology of thermoregulation.

Background: Certified athletic trainers recognize and treat athletes with EHIs, often in high-risk environments. Although the proper recognition and successful treatment strategies are well documented, EHIs continue to plague athletes, and exertional heat stroke remains one of the leading causes of sudden death during sport. The recommendations presented in this document provide athletic trainers and allied health providers with an integrated scientific and clinically applicable approach to the prevention, recognition, treatment of, and return-to-activity guidelines for EHIs. These recommendations are given so that proper recognition and treatment can be accomplished in order to maximize the safety and performance of athletes.

Recommendations: Athletic trainers and other allied health care professionals should use these recommendations to establish onsite emergency action plans for their venues and athletes. The primary goal of athlete safety is addressed through the appropriate prevention strategies, proper recognition tactics, and effective treatment plans for EHIs. Athletic trainers and other allied health care professionals must be properly educated and prepared to respond in an expedient manner to alleviate symptoms and minimize the morbidity and mortality associated with these illnesses.

Key Words: heat cramps, heat syncope, heat exhaustion, heat injury, heat stroke, dehydration

The prevention, recognition, and treatment of exertional heat illnesses (EHIs) are core components of sports medicine services at all levels of sport. The risk of EHI is ever present during exercise in the heat but can also occur in "normal" environmental conditions. Our current knowledge base has allowed us to greatly enhance the level of care that can be provided for athletes with these medical conditions. This document serves as the current position statement for the National Athletic Trainers' Association (NATA) and replaces the document that was published in 2002.[1]

The care of exertional heat-stroke (EHS) patients has come a long way in the past millennia. We now possess the knowledge to nearly assure survival from this potentially fatal injury if EHS is quickly and appropriately recognized and treated at the time of collapse.[2,3] Additionally, our knowledge base and proven management protocols allow us to establish effective prevention and management strategies to minimize the risk of and improve the outcome

from EHS, thereby affecting public health via policy creation and modification.

DEFINITIONS OF EHIs

Exercise-Associated Muscle Cramps

Exercise-associated muscle cramps (EAMCs) are sudden or sometimes progressively and noticeably evolving, involuntary, painful contractions of skeletal muscle during or after exercise.[4,5] *Heat cramps* is a popular but technically inappropriate term for a certain category of EAMCs because they are not directly related to an elevated body temperature,[5,6] do not readily occur after passive heating at rest, and can present during exercise in warm or even cool[6–8] and temperature-controlled conditions,[9] although extensive sweating is typical. The signs and symptoms of incipient EAMCs can be described as *tics*, *twinges*, *stiffness*, *tremors*, or *contractures*, but these terms refer to conditions that are typically painless and do not demonstrate muscle activity on electromyography, unlike full-blown EAMCs.[10] The cause of EAMCs is not fully confirmed; proposed contributing factors and conditions include dehydration,[5] electrolyte imbalances,[5,11] altered neuromuscular control,[4] fatigue, or any combination of these factors.[5–10]

Heat Syncope

Heat syncope, or orthostatic dizziness, often occurs in unfit or heat-unacclimatized persons who stand for a long period of time in the heat or during sudden changes in posture in the heat, especially when wearing a uniform or insulated clothing that encourages and eventually leads to maximal skin vasodilation. This condition is often attributed to dehydration, venous pooling of blood, reduced cardiac filling, or low blood pressure with resultant cerebral ischemia.[12] Heat syncope usually occurs during the first 5 days of unaccustomed heat exposure (eg, during the preseason), before the blood volume expands and cardiovascular adaptations are complete, and in those with heart disease or taking diuretics.[13]

Heat Exhaustion

Heat exhaustion is the inability to effectively exercise in the heat, secondary to a combination of factors, including cardiovascular insufficiency, hypotension, energy depletion, and central fatigue.[14] This condition is manifested by an elevated core body temperature (usually $<$40.5°C) and is often associated with a high rate or volume of skin blood flow, heavy sweating, and dehydration.[15] It occurs most frequently in hot or humid (or both) conditions, but it can also occur in normal environmental conditions with intense physical activity. Heat exhaustion most often affects heat-unacclimatized or dehydrated individuals with a body mass index $>$27 kg/m.[16] By definition, absent from heat exhaustion are end-organ damage, which would indicate heat injury (eg, renal insufficiency, rhabdomyolysis, or liver injury), and significant central nervous system (CNS) dysfunction with marked temperature elevation ($>$40.5°C [105°F]), which would indicate the possibility of EHS.

Exertional Heat Injury

Heat injury is a moderate to severe heat illness characterized by organ (eg, liver, renal) and tissue (eg, gut, muscle) injury associated with sustained high body temperature resulting from strenuous exercise and environmental heat exposure. Body temperature is usually but not always greater than 40.5°C (105°F).[17,18]

Exertional Heat Stroke

Exertional heat stroke is the most severe heat illness. It is characterized by neuropsychiatric impairment and a high core body temperature, typically $>$40.5°C (105°F).[16,19] This condition is a product of both metabolic heat production and environmental heat load and occurs when the thermoregulatory system becomes overwhelmed due to excessive heat production (ie, metabolic heat production from the working muscles) or inhibited heat loss (ie, decreased sweating response, decreased ability to evaporate sweat) or both. Although this illness is most likely to occur in hot and humid weather, it can manifest with intense physical activity in the absence of extreme environmental conditions. The first sign of EHS is often CNS dysfunction (eg, collapse, aggressiveness, irritability, confusion, seizures, altered consciousness).[19] A medical emergency, EHS can progress to a systemic inflammatory response and multi-organ system failure unless promptly and correctly recognized and treated. The risks of morbidity and mortality increase the longer an individual's body temperature remains elevated above the critical threshold ($>$40.5°C [105°F]) and are significantly reduced if body temperature is lowered promptly.[20]

RECOMMENDATIONS

The NATA advocates the following prevention, recognition, and treatment strategies for EHIs. These recommendations are presented to help certified athletic trainers and other health care providers maximize health, safety, and sport performance. However, individual responses to physiologic stimuli and environmental conditions vary widely. Therefore, these recommendations do not guarantee full protection from exertional heat-related illnesses but could mitigate the risks associated with athletic participation and physical activity. These recommendations and prevention strategies should be carefully considered and implemented by certified athletic trainers and the health care team as part of an overall strategy for the prevention and treatment of EHIs. The strength of each recommendation follows the Strength of Recommendation taxonomy (SORT; Table 1).[21]

Prevention

1. Conduct a thorough, physician-supervised preparticipation medical screening before the start of the season to identify athletes with risk factors for heat illness or a history of heat illness (Table 2).[22,23] *Strength of recommendation: C*
2. Individuals should be acclimatized to the heat gradually over 7 to 14 days.[22–26] Heat acclimatization involves progressively increasing the intensity and duration of physical activity and phasing in protective equipment (if

Table 1. Strength of Recommendation Taxonomy (SORT)[a]

Strength of Recommendation	Definition
A	Recommendation based on consistent and good quality experimental evidence (morbidity, mortality, exercise and cognitive performance, physiologic responses).
B	Recommendation based on inconsistent or limited quality experimental evidence.
C	Recommendation based on consensus; usual practice; opinion; disease-oriented evidence[b]; case series or studies of diagnosis, treatment, prevention, or screening; or extrapolations from quasi-experimental research.

[a] Reprinted with permission from Ebell MH, Siwek J, Weiss BD, et al, Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature, 2004;69(3):548–556, *Am Fam Physician*. Copyright 2004 American Academy of Family Physicians. All Rights Reserved.[14]

[b] Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptoms improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (eg, blood pressure, blood chemistry, physiologic function, pathologic finding).

applicable). If heat acclimatization is not maintained, the physiologic benefits provided by this process will decay within 3 weeks.[24–26] The first 2–3 weeks of preseason practice typically present the greatest risk of EHI, particularly in equipment-intensive sports.[26,27–29] All possible preventive measures should be used during this time to address this high-risk period (Figure 1). *Strength of recommendation: B*

3. Athletes who are currently sick with a viral infection (eg, upper respiratory tract infection or gastroenteritis) or other illness or have a fever or serious skin rash should not participate until the condition is resolved.[16,27,30] Even after symptoms resolve, the athlete may still be susceptible to heat illness and should be observed carefully upon return to exercising in the heat. *Strength of recommendation: B*
4. Individuals should maintain euhydration and appropriately replace fluids lost through sweat during and after games and practices (see the NATA position statement on fluid replacement in athletes[31]). Players should have free access to readily available fluids at all times, not just during designated breaks. Instruct them to eat or drink appropriate sodium-containing fluids and foods to help replace sodium losses in sweat and urine and to enhance hydration (ie, water retention and distribution). The aims of fluid consumption or replacement are to prevent a body mass loss of more than 2% (as measured before and after the practice or game) and to keep morning urine light in color.[31,32] These strategies may reduce the risk of acute and chronic significant dehydration and decrease the risk of EHI.[27,31–34] *Strength of recommendation: B*
5. The sports medicine staff must educate relevant personnel (ie, coaches, administrators, security guards, emergency medical services [EMS] staff, athletes) on preventing and recognizing EHI and, in particular, EHS.[35,36] Signs and symptoms of a medical emergency should be reviewed, and every institution should have and personnel should practice an emergency action plan specific to each practice and game site. Review and rehearsal of the emergency action plan should include all relevant members of the sports medicine team (ie, coaches, athletic trainers, EMS). *Strength of recommendation: C*
6. Appropriate medical care must be available, and all personnel must be familiar with EHI prevention, recognition, and treatment.[35–37] Certified athletic trainers and other health care providers covering practices or events are the primary providers of medical care for athletes who display signs or symptoms of EHI and have the authority to restrict an athlete from participating if EHI is suspected or to refer the athlete for a significant EHI condition. *Strength of recommendation: C*
7. When environmental conditions warrant, a cold-water or ice tub and ice towels should be available to immerse or soak a patient with a suspected heat illness.[33,37] Immediate whole-body cooling is essential for treating EHI and EHS in particular. Onsite facilities are needed for immediate treatment. *Strength of recommendation: B*
8. The assessment of rectal temperature is the clinical gold standard for obtaining core body temperature of patients with EHS[38] and the medical standard of practice and accepted protocol. No other field-expedient methods of obtaining core body temperature (eg, oral, axillary, tympanic, forehead sticker, temporal) are valid or reliable after intense exercise in the heat, and they may lead to inadequate or inappropriate treatment, thereby endangering a patient's health.[38–41] Parents, administrators, coaches, and student-athletes should be educated ahead of time that this procedure will be used for heat-illness emergencies, especially in patients suspected of having heat exhaustion or EHS. Esophageal and gastrointestinal

Table 2. Sample Preparticipation Physical Examination Questions Related to Exertional Heat Stroke[69]

1. Have you ever previously been diagnosed with exertional heat stroke? If yes
   a. How long ago?
   b. Have you had any complications since then?
   c. How long did it take you to return to full participation?
   d. Did you have any complications upon your return to play?
   e. Was an exercise heat tolerance test conducted to assess your thermoregulatory capacity?
2. Have you ever been diagnosed with heat exhaustion? If yes
   a. When?
   b. How many times?
3. Have you ever had trouble or complications from exercising in the heat (eg, feeling sick, throwing up, dizzy, lack of energy, decreased performance, muscle cramps)?
4. How much training have you been doing recently (in the past 2 weeks)? Has this been performed in warm or humid weather?
5. Have you been training during the last 2 months? Would you say you are in poor, good, or excellent condition?
6. Describe your drinking habits. (Are you conscious of how much you consume? Is your urine consistently dark?)
7. Would you consider yourself a heavy or a salty sweater?
8. How many hours of sleep do you get per night? Do you sleep in an air-conditioned room?
9. Do you take any supplements or ergogenic aids?

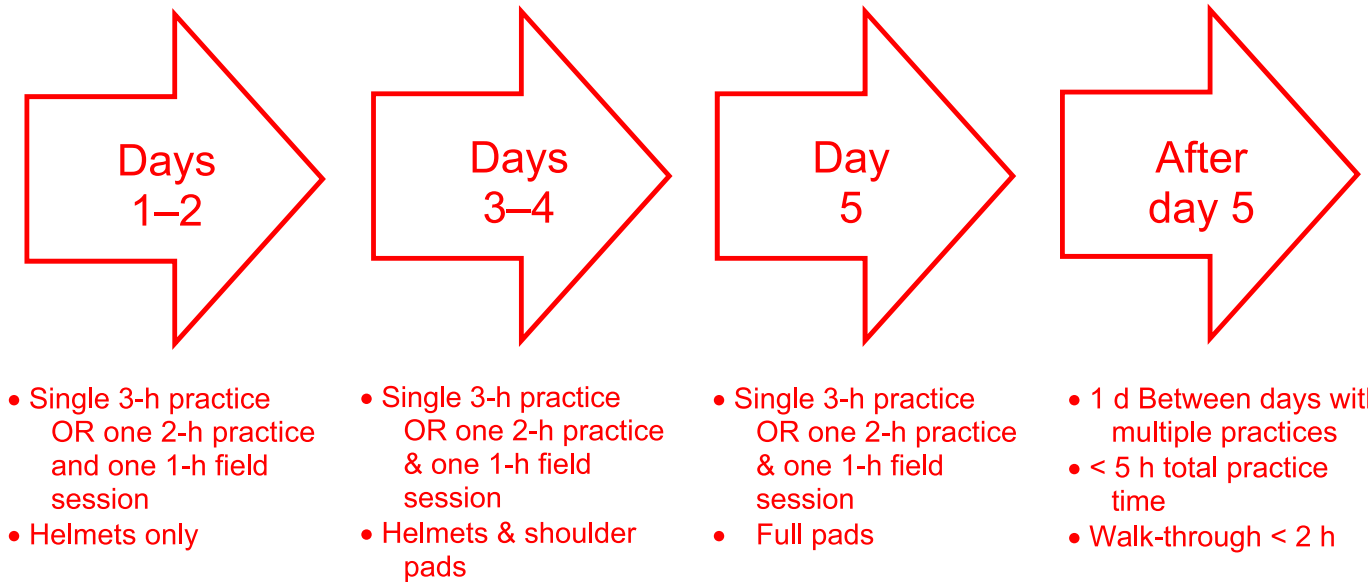

Figure 1. National Collegiate Athletic Association heat-acclimatization guidelines.

(via ingestible thermistor) measurements may be appropriate alternatives for temperature assessment but require advanced training for the former and careful planning for the latter. Under all circumstances in which EHS is possible, a rectal temperature assessment should be able to be obtained. *Strength of recommendation: A*

9. Because the effects of heat are cumulative, athletes should be encouraged to sleep at least 7 hours per night in a cool environment; eat a balanced diet; and properly hydrate before, during, and after exercise.[16] Individuals should also be advised to rest in a cool environment during periods of inactivity (eg, off days, between sessions on double-practice days) to maximize recovery. Rest periods should incorporate meal times and allow 2 to 3 hours for food, fluids, electrolytes (primarily sodium and chloride), and other nutrients to be digested and absorbed before the next practice or competition. *Strength of recommendation: C*
10. To anticipate potential problems, a preseason heat-acclimatization policy should be developed for organized sports and event guidelines formulated for hot, humid weather conditions based on the type of activity and wet-bulb globe temperature (WBGT).[23,26] In stressful environmental conditions, particularly during the first 2–3 weeks of preseason practice, activity should be delayed or rescheduled or the practice session shortened to reduce the risk to participants. Special attention should be given to practice drills that involve high-intensity activity and full protective equipment worn by players, as these factors may exacerbate the amount of heat stress on the body. *Strength of recommendation: B*
11. Individuals who may be particularly susceptible to EHI must be identified.[42–45] They should be closely monitored during stressful environmental conditions, and preventive steps should be taken.[45,46] In addition, emergency supplies and equipment (eg, tubs for cold-water immersion [CWI], rectal thermometer) should be onsite, easily accessible, and in good working order to allow for immediate intervention and treatment if needed. *Strength of recommendation: B*
12. Rest breaks should be planned and the work-to-rest ratio modified to match the environmental conditions and the intensity of the activity.[45–47] Breaks should be in the shade or in a predetermined cooling zone and should allow enough time for all athletes to consume fluids. Additionally, players should be permitted to remove equipment (eg, helmets) during rest periods. *Strength of recommendation: B*
13. The use of dietary supplements and other substances that have a dehydrating effect, increase metabolism, or affect body temperature and thermoregulation is discouraged.[48] Because supplements may increase the risk of EHI, their use should be carefully monitored. *Strength of recommendation: C*
14. Minimal experimental evidence exists regarding the most effective method of preventing EAMCs due to the variety of causes. Supplemental sodium ingestion and fluid monitoring[9] or neuromuscular reeducation[49] may help to prevent EAMC recurrences. Clinicians should identify the patient's unique intrinsic (eg, hydration, acclimatization, biomechanics, training status) and extrinsic (eg, climate conditions, exercise intensity) risk factors that preceded EAMCs before implementing a prevention strategy. *Strength of recommendation: C*

Recognition

Exercise-Associated Muscle Cramps.

15. A patient experiencing EAMCs will likely show 1 or more of the following signs and symptoms: visible cramping in part or all of the muscle or muscle groups, localized pain, dehydration, thirst, sweating, or fatigue.[4,5,50] *Strength of recommendation: C*
16. A thorough medical history should be obtained to distinguish muscle cramping as a result of an underlying clinical condition (eg, sickle cell trait) from EAMCs.[50] The latter is often preceded by subtle muscle twitching,[4] whereas the former is not. *Strength of recommendation: C*
17. Most EAMCs related to overload or fatigue tend to be short in duration (less than 5 minutes) and mild in

severity.[7,51] However, some EAMCs severely affect athletic performance and as a result, prohibit further exercise; require further medical attention to resolve; or elicit soreness for several days.[7,49–51] *Strength of recommendation: B*

Heat Syncope.

18. A patient who experiences a brief episode of fainting associated with dizziness, tunnel vision, pale or sweaty skin, and a decreased pulse rate while standing in the heat or after vigorous exercise (with a relatively low rectal temperature [<39°C]) is likely experiencing heat syncope.[12] However, responsiveness, breathing, and pulse must be assessed to rule out a cardiac event, which can present with similar signs and symptoms but is a more serious condition. *Strength of recommendation: B*
19. A thorough medical history and physical examination should be performed to eliminate any other medical conditions that could cause syncope. *Strength of recommendation: C*

Exertional Heat Exhaustion.

20. Heat exhaustion may be present if the patient demonstrates excessive fatigue, faints, or collapses with minor cognitive changes (eg, headache, dizziness, confusion) while performing physical activity,[15] yet the athletic trainer should assess the patient's CNS function by noting any bizarre behavior, hallucinations, altered mental status, confusion, disorientation, or coma that may indicate a more serious condition such as EHS. Other signs and symptoms of exertional heat exhaustion may include fatigue, weakness, dizziness, headache, vomiting, nausea, lightheadedness, low blood pressure, and impaired muscle coordination. *Strength of recommendation: B*
21. It is strongly recommended that a rectal temperature be obtained to differentiate exertional heat exhaustion from the more serious EHS. With heat exhaustion, core body temperature (measured rectally) is usually less than 40.5°C (105°F), a key characteristic that differentiates it from EHS. *Strength of recommendation: A*

Exertional Heat Stroke.

22. The 2 main diagnostic criteria for EHS are CNS dysfunction and a core body temperature greater than 40.5°C (105°F).[16,19,52] However, if a suspected EHS victim exhibits CNS dysfunction even though the rectal temperature is slightly lower (ie, 40°C [104°F]), it is prudent to assume the patient is suffering from EHS and begin the appropriate treatment. After initial collapse, recognition is often delayed, and the patient may begin to cool passively, dropping below the 40.5°C (105°F) threshold. Rectal temperature thermometry is the only method of obtaining an immediate and accurate measurement of core body temperature. Other devices, such as oral, axillary, aural canal, tympanic, forehead sticker, and temporal artery thermometers, inaccurately assess the body temperature of an exercising person.[38–41] A delay in accurately assessing temperature during diagnosis may also explain a body temperature that is lower than expected. *Strength of recommendation: A*
23. Because immediate treatment is vital in EHS, it is important to not waste time by substituting an invalid method of temperature assessment if rectal thermometry is not available. Instead, the practitioner should rely on other key diagnostic indicators (ie, CNS dysfunction, circumstances of the collapse). If EHS is suspected, CWI (or another rapid cooling mechanism if CWI is not available) should be initiated immediately. *Strength of recommendation: C*
24. In a patient suspected of having EHS, CNS function should be assessed. Signs and symptoms can include disorientation, confusion, dizziness, loss of balance, staggering, irritability, irrational or unusual behavior, apathy, aggressiveness, hysteria, delirium, collapse, loss of consciousness, and coma. In some cases, a lucid interval may be present; however, if EHS is present, the patient will likely deteriorate quickly. *Strength of recommendation: B*
25. Other signs and symptoms of EHS that may be present include dehydration, hot and wet skin, hypotension, and hyperventilation. Most patients with EHS have hot, sweaty skin as opposed to those with the classical type of heat stroke (the passive condition that typically affects children and the elderly), who present with dry skin. (Table 3). *Strength of recommendation: B*

Heat Injury.

26. Heat injury is a moderate to severe heat illness characterized by end-organ damage but the absence of the profound CNS dysfunction often found with EHS.[17,18] Evaluation usually reveals very dark (cola-colored) urine, severe muscle pain, and abnormal blood chemistry levels. *Strength of recommendation: B*

Treatment

Exercise-Associated Muscle Cramps.

27. The immediate treatment for acute EAMCs related to muscle overload or fatigue is rest and passive static stretching of the affected muscle until cramps abate.[7,51,53] Icing, massage, or both may also help relieve some of the discomfort after EAMCs.[5] For EAMCs related to excessive sweating and a suspected whole-body sodium deficit, the patient must ingest sodium-containing fluids (preferably) or foods (or both) to help return the body to normal fluid, electrolyte, and energy distribution. *Strength of recommendation: B*
28. Fluid absorption, retention, and distribution are enhanced by beverages that contain sodium and carbohydrates. A high-sodium product (eg, salt packet) may be added to a beverage to help offset sodium lost via exercise-induced sweating. Similarly, small volumes (eg, 1 mL per 1 kg body weight) of a salty solution such as pickle juice may be consumed, if tolerated, without negatively affecting ad libitum water ingestion,[54] plasma electrolyte concentrations,[55] or thirst or causing nausea or stomach fullness.[54] *Strength of recommendation: B*
29. Patients with EAMCs are normally conscious and responsive and have normal vital signs.[50] Thus, clinicians can provide fluids orally to a patient suffering from EAMCs who is compliant and tolerating fluid intake. The use of intravenous fluids should be considered if the patient is noncompliant or unable to tolerate fluids.[5] *Strength of recommendation: A*
30. Patients with recurring EAMCs should undergo a thorough medical screening to rule out more serious

Table 3. Clinical Distinctions of Exertional Heat Illnesses

Characteristic	Heat Illness			
	Exercise-Associated Muscle (Heat) Cramps	Heat Syncope	Heat Exhaustion	Exertional Heat Stroke
Description	Acute, painful, involuntary muscle contractions presenting during or after exercise	Collapsing in the heat, resulting in loss of consciousness	Inability to continue exercise due to cardiovascular insufficiency	Severe hyperthermia leading to overwhelming of the thermoregulatory system
Physiologic cause	Dehydration, electrolyte imbalances, and/or neuromuscular fatigue	Standing erect in a hot environment, causing postural pooling of blood in the legs	High skin blood flow, heavy sweating, and/or dehydration, causing reduced venous return	High metabolic heat production and/or reduced heat dissipation
Primary treatment factors	Stop exercising, provide sodium-containing beverages	Lay patient supine and elevate legs to restore central blood volume	Cease exercise, remove from hot environment, elevate legs, provide fluids	Immediate whole-body cold-water immersion to quickly reduce core body temperature
Recovery	Often occurs within minutes to hours	Often occurs within hours	Often occurs within 24 h; same-day return to play not advised	Highly dependent on initial care and treatment; further medical testing and physician clearance required before return to activity

neuromuscular conditions (eg, fatigue, hydration level, improper nutrition).[50] *Strength of recommendation: C*

Heat Syncope.

31. The clinician should move the patient to a shaded area, monitor vital signs, elevate the legs above the level of the heart, cool the skin, and rehydrate.[12] *Strength of recommendation: C*

Exertional Heat Exhaustion.

32. Removing any excess clothing and equipment increases the evaporative surface of the skin and facilitates cooling. *Strength of recommendation: C*
33. The patient should be moved to a cool or shaded area. Further body cooling should be accomplished via fans or ice towels if necessary. *Strength of recommendation: C*
34. While monitoring vital signs, the clinician should place the patient in the supine position with legs elevated above the level of the heart to promote venous return.[15,16,56] *Strength of recommendation: C*
35. If intravenous fluids are needed or if recovery is not rapid (within 30 minutes of initiation of treatment) and uneventful, fluid replacement should begin and the patient's care transferred to a physician. If the condition worsens during or after treatment, EMS should be activated.[15,16] Additionally, rectal temperature should be obtained; if >40.5°C (105°F), the patient should be treated for EHS. *Strength of recommendation: C*

Exertional Heat Stroke.

36. For any EHS patient, the goal is to lower core body temperature to less than 38.9°C (102°F) within 30 minutes of collapse.[20] Body cooling serves 2 purposes: returning blood flow from the skin to the heart and lowering core body temperature by reducing the hypermetabolic state of the organs. The length of time the core body (and particularly the brain) is above the critical temperature threshold (40.5°C [105°F]) dictates morbidity and the risk of death from EHS (Figure 2).[57,58] *Strength of recommendation: B*
37. When EHS is suspected, the patient's body (trunk and extremities) should be quickly immersed in a pool or tub of cold water. Removing excess clothing and equipment will enhance cooling by maximizing the surface area of the skin. However, because removing excess clothing and equipment can be time consuming, CWI should begin immediately and equipment should be removed while the patient is in the tub (or while temperature is being assessed or the tub is being prepared).[59] Rectal temperature and other vital signs should be monitored during cooling every 5 to 10 minutes if a continuous monitoring device is not available.[20,60] *Strength of recommendation: B*
38. Cold-water immersion up to the neck is the most effective cooling modality for patients with EHS.[57] The water should be approximately 1.7°C (35°F) to 15°C (59°F) and stirred continuously to maximize cooling. The patient should be removed when core body temperature reaches 38.9°C (102°F) to prevent overcooling (Table 4).[60] *Strength of recommendation: A*
39. Although cooling rates may vary, the cooling rate for CWI will be approximately 0.2°C/min (0.37°F/min) or about 1°C every 5 minutes (or 1°F every 3 minutes) when considering the entire immersion period from postcollapse to 38.9°C (102°F).[20,57,58] *Strength of recommendation: B*
40. If full-body CWI is not available, partial-body immersion (ie, torso) with a small pool or tub and other modalities, such as wet ice towels rotated and placed over the entire body or cold-water dousing with or without fanning, may be used but are not as effective as CWI.[61,62] *Strength of recommendation: B*
41. If a physician is onsite (as in a mass medical tent situation) and can manage the EHS, then transportation to a medical facility may not be necessary if cooling occurred immediately (ie, if the duration above 40°C [104°F] was less than 30 minutes) and the patient is asymptomatic 1 hour postcooling. If a physician is not present but other medical staff (eg, AT, EMS, nurse) are onsite, aggressive cooling should continue until the patient's temperature is 39°C (102.8°F). When medical staff is onsite, all patients with EHS should be cooled first and transported second. However, when medical staff is not present and EHS is suspected, then the coaching

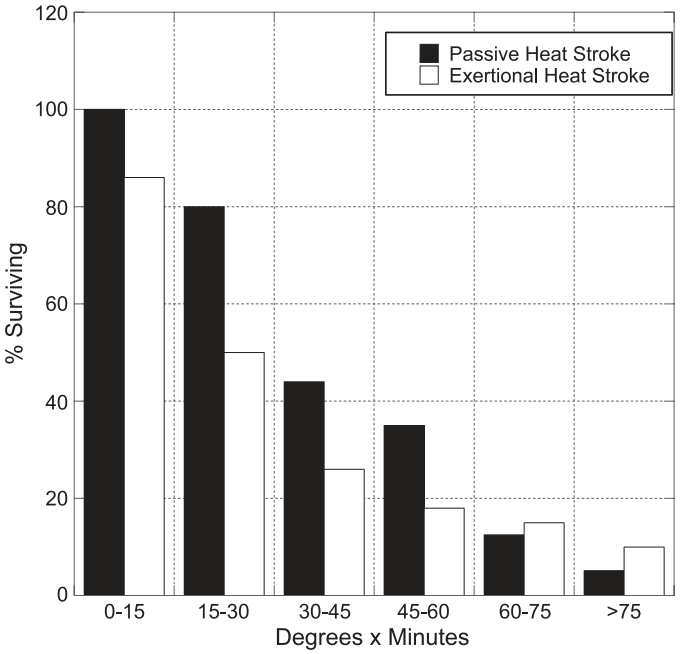

Figure 2. Relationship between severity of hyperthermia and rat survivability. Reprinted with permission. Casa DJ, Kenny JP, Taylor NAS. Immersion treatment for exertional hyperthermia: cold or temperate water? *Med Sci Sports Exerc.* 2010;42(7):1246–1252. Promotional and commercial use of the material in print, digital, or mobile-device format is prohibited without the permission from publisher Wolters Kluwer Health. Please contact lwwjournalpermissions@wolterskluwer.com for further information.

staff/supervisors should implement cooling until medical assistance arrives. *Strength of recommendation: B*

42. Policies and procedures for cooling patients before transport to the hospital must be explicitly stated in an emergency action plan and shared with potential EMS responders so that treatment of EHS by all medical professionals is coordinated (Figure 3). *Strength of recommendation: B*

Return to Activity

43. In cases of EAMCs or heat syncope, the athletic trainer should monitor the patient's condition until signs and symptoms are no longer present. *Strength of recommendation: C*
44. In patients with heat exhaustion, same-day return to activity is not recommended and should be avoided.[15,56] *Strength of recommendation: C*
45. Many patients with EHS are cooled effectively and sent home the same day[63]; they may be able to resume modified activity within 1 month with a physician's clearance. However, when treatment is delayed (ie, not provided within 30 minutes), patients may experience residual complications for months or years after the event. *Strength of recommendation: C*
46. Most guidelines suggest that a patient recovering from EHS be asymptomatic with normal blood-work results (renal and hepatic panels, electrolytes, and muscle enzyme levels) before a gradual return to activity is initiated.[64] Unfortunately, few evidence-based strategies have been developed to determine recovery of the thermoregulatory system,[65] so the medical professional must use clinical cues such as ongoing signs and symptoms, responses to a standard exercise heat-tolerance test, responses to gradually increasing exercise demands, and ability to acclimatize to the heat to make return-to-play decisions. *Strength of recommendation: C*
47. In all cases of EHS, after the patient has completed a 7- to 21-day rest period, demonstrated normal blood-work results, and obtained physician clearance, he or she may begin a progression of physical activity, supervised by the athletic trainer or other medical professional with knowledge of EHS treatment and care, from low intensity

Table 4. Guidelines for Implementing Cold-Water Immersion for a Patient With Exertional Heat Stroke

1. Initial response. Once exertional heat stroke is suspected, prepare to cool the patient and contact emergency medical services.
2. Prepare for ice-water immersion. On the playing field or in close proximity, half-fill a stock tank or wading pool with water and ice (make sure there is a sufficient water source).
   a. The tub can be filled with ice and water before the event begins (or have the tub half-filled with water and keep 3 to 4 coolers of ice next to the tub; this prevents having to keep the tub cold throughout the day.
   b. Ice should cover the surface of the water at all times.
   c. If the athlete collapses near the athletic training room, a whirlpool tub or cold shower may be used.
3. Determine vital signs. Immediately before immersing the patient, obtain vital signs.
   a. Assess core body temperature with a rectal thermistor.
   b. Check airway, breathing, pulse, and blood pressure.
   c. Assess the level of central nervous system dysfunction.
4. Begin ice-water immersion. Place the patient in the ice-water–immersion tub. Medical staff, teammates/coaches, and volunteers may be needed to assist with entry to and exit from the tub.
5. Total-body coverage. Cover as much of the body as possible with ice water while cooling.
   a. If full-body coverage is not possible due to the tub size, cover the torso as much as possible.
   b. To keep the patient's head and neck from going under water, an assistant may hold him or her under the axillae with a towel or sheet wrapped across the chest and under the arms.
   c. Place an ice/wet towel over the head and neck while body is being cooled in the tub.
   d. Use a water temperature under 15°C (60°F).
6. Vigorously circulate the water. During cooling, water should be continuously circulated or stirred to enhance the water-to-skin temperature gradient, which optimizes cooling. Have an assistant stir the water during cooling.
7. Continue medical assessment. Vital signs should be monitored at regular intervals.
8. Fluid administration. If a qualified medical professional is available, an intravenous fluid line can be placed for hydration and support of cardiovascular function.
9. Cooling duration. Continue cooling until the patient's rectal temperature lowers to 38.9°C (102°F).
   a. If rectal temperature cannot be measured and cold-water immersion is indicated, cool for 10–15 min and then transport to a medical facility.
   b. An approximate estimate of cooling via cold-water immersion is 1°C for every 5 min and 1°C for every 3 min (if the water is aggressively stirred). For example, someone in the tub for 15 min would cool approximately 3°C or 5°C during that time.
10. Patient transfer. Remove the patient from the immersion tub only after rectal temperature reaches 38.9°C (102°F) and then transfer to the nearest medical facility via emergency medical services as quickly as possible.

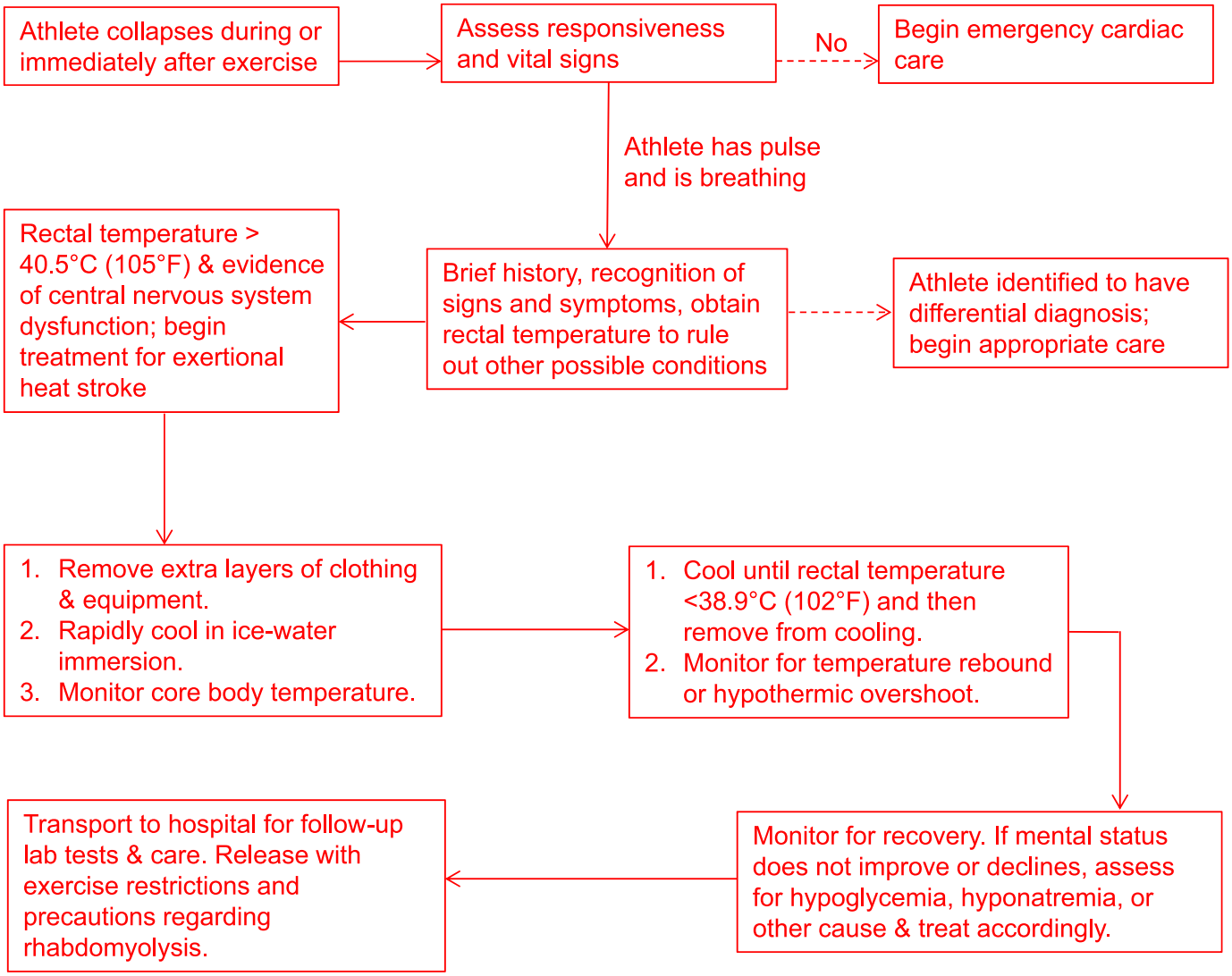

Figure 3. Algorithm for treatment of exertional heat stroke.

to high intensity and increasing duration in a temperate environment, with equipment added gradually where indicated. Also, a graded progression of heat acclimatization, while monitoring for signs and symptoms of EHI, should be completed. The ability to progress depends largely on the treatment provided, and in some rare cases, full recovery may not be possible. Rectal temperature and heart rate should be monitored during these activities, and if the patient experiences any side effects or negative symptoms with training, the progression should be slowed, delayed, or stopped.[65,66] *Strength of recommendation: C*

48. Although structured guidelines for return to play after EHS in athletics are lacking, the US military has adopted effective recommendations for the proper progression of return to duty after an episode of EHS. The main considerations are treating any associated sequelae and, if possible, identifying the cause of EHS, so that future episodes can be prevented.[65–67] As evidence-based medicine research has advanced, the role of exercise heat-tolerance testing has gained favor as a common-sense approach: a patient who has a poor test result should not increase activity at that point. However, the significance of a normal test result and its relationship with clearance to return to play still need to be refined and evaluated. In either circumstance, monitoring the physiologic response to series of challenging exercise heat exposures is a large step forward in our delivery of health care to the EHS patient who is recovering and working toward a return to physical activity as a laborer, soldier, or athlete. This method has proved effective within the Israeli military[68] and the US military and at the Korey Stringer Institute, and it supports many of the considerations put forth by the American College of Sports Medicine and US military.[65,67,69] *Strength of recommendation: C*

BACKGROUND AND REVIEW OF THE LITERATURE

Thermoregulation

Thermoregulation is a complex interaction of the CNS, the cardiovascular system, and the skin to maintain a core body temperature of approximately 37°C (98.6°F).[17,34,70,71] The CNS temperature-regulation center, located in the

hypothalamus, is where the core temperature setpoint is determined. The hypothalamus receives information regarding core body temperature and skin temperature from peripheral skin receptors and the circulating blood. This interaction regulates core body temperature via an open-ended feedback loop similar to a home thermostat system. Based on the peripheral feedback sent to the hypothalamus, the body adjusts accordingly to initiate the appropriate heat-transfer responses. If core temperature falls below the normal setpoint, peripheral vasoconstriction and shivering responses increase core body temperature, whereas if core temperature rises above the normal setpoint, cutaneous vasodilation and increased sweating occur to dissipate heat.[70,71]

Core body temperature is determined by metabolic heat production and the transfer of body heat to and from the surrounding environment by the following heat-balance equation[71]:

$$S = M(\pm \text{ work}) - E \pm R \pm C \pm K, \quad (1)$$

where S is the amount of stored heat, M is the metabolic heat production, E is the evaporative heat loss, R is the heat gained or lost by radiation, C is the heat lost or gained by convection, and K is the heat lost or gained by conduction. Basal metabolic heat production while fasting and at absolute rest is approximately 60 to 70 kcal/h for an average adult, with 50% of the heat being produced by internal organs.[72] Metabolic heat produced by intense exercise may approach 1000 kcal/h, with more than 90% of the heat resulting from metabolism in muscles.[72] Heat is further gained or lost by 1 or more of the following mechanisms.[72]

Radiation: Heat is transferred to or from an object or body via electromagnetic radiation (ie, sunlight) from higher to lower energy surfaces.

Conduction: Heat is transferred from warmer to cooler objects through direct physical contact (eg, ice packs).

Convection: Heat is transferred to or from the body to surrounding fluid or air (eg, moving air from a fan or immersion in water).

Evaporation: Heat is transferred via the vaporization of sweat. This is the most efficient means of heat transfer. The evaporation of sweat from the skin depends on the water saturation of the air (ie, humidity level) and the velocity of the moving air (ie, wind speed).[17,30,70–73] The effectiveness of evaporation for heat loss from the body diminishes rapidly when the humidity level is high.

Exercise-Associated Muscle Cramps

The most common EHI experienced by athletes is EAMCs.[74] They afflict adolescents,[9] adult athletes,[7,51,74,75] soldiers, and industrial workers. They are seemingly unpredictable, though affected athletes often report muscle twinges before they experience full-blown, debilitating muscle cramping. Probably because spinal inhibition is weakest when a muscle contracts forcefully while shortened, EAMCs usually occur when muscles are in this position.[76] Although they may occur in any muscle, EAMCs related to muscle overload or fatigue tend to affect exercising (or constantly loaded) muscles, especially those that cross 2 joints in the lower extremities (eg, gastrocnemius, hamstrings).[7] Patients experiencing EAMCs typically display a transient inability to continue normal activity and may have muscle soreness for days postcramping.[50]

Their cause is controversial,[4,10] but a growing body of experimental,[76–79] quasiexperimental,[6–8,51,75] and case[49] studies suggest that EAMCs are not the result of dehydration or electrolyte losses. Although athletes prone to EAMCs may have substantial fluid (2 to 3.4 L/h) and sodium (up to 5 g or far more in a single session) losses,[9,11] the volume of fluid ingested,[11] postexercise body weights,[7,8,11] and gross sweat losses[11] are often comparable with those of noncramping athletes. These findings underscore that such measures (or blood sodium concentration) do not necessarily indicate a whole-body sodium deficit. Potential risk factors for EAMCs consistent across several prospective cohort studies[7,51,75,80] include a history of EAMCs; faster competition performance times; and prior muscle, tendon, or ligament injury. In contrast, stretching history, muscle flexibility, training frequency or volume, height, age, body mass index, weight, and sex tend not to be adequate predictors of EAMC occurrence.[7,51,75,80]

The most effective treatment for acute EAMCs is static stretching of the affected muscle until the cramp subsides.[7,51,53] Stretching reduces the activity of cramping muscles[53] and may relieve cramps by increasing the inhibition produced by the Golgi tendon organs[4,76] or the physical separation of contractile proteins (or both).[53] The effectiveness of chronic or acute static stretching as prophylaxis against future EAMC episodes is unknown. Those patients with EAMCs related to a whole-body sodium deficit must be promptly treated with a high-salt solution, either orally or intravenously. However, it is important to note that this treatment will not result in immediate relief of muscle cramping because of the time necessary to properly absorb sodium.

No well-designed, controlled cohort or experimental studies have compared the effectiveness of EAMC prophylactics, yet some case studies suggest that fluid and electrolyte monitoring and replacement[9] or neuromuscular reeducation[49] may effectively reduce EAMC recurrence.

Hyperthermia and EHS

Signs and symptoms of hyperthermia include dizziness, confusion, behavioral changes, coordination difficulties, decreased cognitive function, reduced physical performance, and collapse.[15,52,69,71,72,81,82] The residual effects of elevated core body temperature depend on the duration, not necessarily the degree, of the hyperthermia.[46,57,69,82] Moderate exercise-induced hyperthermia is normal and even protective in that it triggers the body's thermoregulatory system. However, with EHS (core body temperature greater than 40.5°C [105°F]), long-term neurologic deficits are possible if the condition is not quickly recognized and treated. When EHS is immediately treated via rapid whole-body cooling and core body temperature is normalized within 30 minutes of collapse, a 100% survival rate with limited or no sequelae has been reported.[57,69]

The fastest way to decrease core body temperature is full-body CWI in a pool or tub (with a water temperature between 1°C [35°F] and 15°C [(59°F]).[57,61,69] Timely (less than 30 minutes from the time of collapse) CWI therapy was associated with a 0% fatality rate in more than 2000

Table 5. Example of Wet-Bulb Globe Temperature (WBGT) Guidelines[a]

WBGT Reading	Activity Guidelines and Rest-Break Guidelines
Under 82.0°F (27.8°C)	Normal activities: provide ≥3 separate rest breaks/h of minimum duration 3 min each during workout.
82.0–86.9°F (27.8°C–30.5°C)	Use discretion for intense or prolonged exercise. Watch at-risk players carefully. Provide ≥3 separate rest breaks/h of minimum duration 4 min each.
87.0°F–89.9°F (30.5°C–32.2°C)	Maximum practice time = 2 h. For football: players restricted to helmet, shoulder pads, and shorts during practice. All protective equipment must be removed for conditioning activities. For all sports: provide ≥4 separate rest breaks/h of minimum duration 4 min each.
90.0–92.0°F (32.2°C–33.3°C)	Maximum length of practice = 1 h. No protective equipment may be worn during practice and there may be no conditioning activities. There must be 20 min of rest breaks provided during the hour of practice.
Over 92.1°F (33.4°C)	No outdoor workouts, cancel exercise, delay practices until a cooler WBGT reading occurs.

Guidelines for hydration and rest breaks

1. Rest time should involve both unlimited hydration intake (water or electrolyte drinks) and rest without any activity involved.
2. For football, helmets should be removed during rest time.
3. The site of the rest time should be a "cooling zone" and not in direct sunlight.
4. When the WBGT reading is greater than 86°F (30°C):
   a. Ice towels and spray bottles filled with ice water should be available at the "cooling zone" to aid the cooling process.
   b. Cold-immersion tubs must be available for practices for the benefit of any player showing early signs of heat illness.

Definitions

1. Practice: The period of time that a participant engages in a coach-supervised, school-approved sport or conditioning-related activity. Practices are timed from the time the players report to the field until they leave the field.
2. Walk-through: This period of time shall last no more than 1 h, is not considered to be a part of the practice-time regulation, and may not involve conditioning or weight-room activities. Players may not wear protective equipment.

[a] Example originates from Georgia High School Athletics Association wet-bulb globe temperature guidelines and is only applicable to those who practice, condition, train, or compete under similar environmental conditions. Guidelines should be region specific and based on the following criteria: (1) environmental conditions, (2) intensity of activity, (3) heat-acclimatization status, (4) equipment and clothing, (5) fitness of individual, and (6) age of participants.

EHS patients in athletics and military settings. Other forms of cooling (eg, cold-water dousing with fans, ice-water towels) may be used if CWI is not available, but these methods decrease core body temperature at a slower rate than does CWI.[61,62,69]

Environmental Risk Factors

Environmental Conditions. Hot and humid environmental conditions can more readily predispose an individual to EHS.* When the environmental temperature is higher than the body's skin temperature, individuals absorb heat from the environment, and their heat loss depends entirely on evaporation.[17,30,71,72] Yet when humidity is also high, evaporative heat loss is severely diminished, which can lead to a rapid rise in core body temperature and an extreme risk for EHS (Table 5).

The environmental factors that influence the risk of heat illness include the ambient temperature, relative humidity (amount of water vapor in the air), air motion (wind speed), and amount of radiant heat from the sun. The relative risk of heat illness can be calculated using the WBGT equation:

$$\begin{aligned}\text{WBGT} = &(\text{wet-bulb temperature} \times 0.7)\\ &+ (\text{black-globe temperature} \times 0.2)\\ &+ (\text{dry-bulb temperature} \times 0.1). \qquad (2)\end{aligned}$$

This equation is used to estimate the risk associated with exercise based on environmental conditions and can be useful for setting local policies regarding environmental heat. The WBGT index has long been used in athletics and by the US military. Using the WBGT index to modify activity in high-risk settings has greatly diminished the occurrence of EHS cases in US Marine Corps recruits. However, due to geographical differences among athletic teams and schools across the United States, the WBGT index may not be the most appropriate tool in determining a universal policy for activity modifications and cancellations.[84] Therefore, caution is necessary when setting protocols based solely on climate due to differences among the various regions of the country. It should be noted that an EHI could occur in seemingly "normal" environmental conditions and, therefore, all appropriate precautions should be taken, especially in the first week of practice (Table 6).

Barriers to Evaporative Heat Loss. Athletic equipment and rubber or plastic suits used for weight loss do not allow water vapor to pass from the skin to the environment and, as a result, inhibit evaporative, convective, and radiant heat loss.[27,42,86,87] Participants who wear equipment that does not allow for heat dissipation are at an increased risk for heat illness. Wearing a helmet is also a risk factor because a significant amount of heat is dissipated through the head. Individuals are most susceptible to EHI during the first week of preseason practices.[29,88,89] Thus, it is important to include a phase-in of equipment as part of the heat-acclimatization period.

Wet-Bulb Globe Temperature the Previous Day and Night. When individuals compete in high WBGT conditions, the risk of EHI increases the following day.[91] This factor appears to be one of the best predictors of EHI and should be considered when planning successive practice sessions. Additionally, individuals who sleep in warm or non–air-conditioned quarters are also at greater risk due to the cumulative effects of heat exposure.

Excessive Clothing or Equipment. Excessive clothing or equipment decreases the body's ability to thermoregulate and may cause greater absorption of radiant heat from the environment.

* *References 17, 22, 23, 30, 33, 71, 72, 83, 85*

Table 6. Risk Factors for Exertional Heat Stroke[69,90]

Extrinsic Risk Factors	Intrinsic Risk Factors
High ambient temperature, solar radiation, and high humidity	High intensity of exercise and/or poor physical conditioning
Athletic gear or uniforms	Sleep loss
Peer or organizational pressure	Dehydration or inadequate water intake
Inappropriate work-to-rest ratios based on intensity, wet-bulb globe temperature, clothing, equipment, fitness, and athlete's medical condition	Use of diuretics or certain medications (ie, antihistamines, diuretics, antihypertensives, attention-deficit hyperactive disorder drugs)
Predisposing medical conditions	Overzealousness or reluctance to report problems, issues, or illnesses
Lack of education and awareness of heat illnesses among coaches, athletes, and medical staff	Inadequate heat acclimatization
No emergency plan to identify and treat exertional heat illnesses	High muscle mass-to-body fat ratio
Minimal access to fluids before and during practice and rest breaks	Presence of a fever
Delay in recognition of early warning signs	Skin disorder

Nonenvironmental Risk Factors

Heat Acclimatization. Heat acclimatization is a physiologic response to repeated heat exposure during exercise over the course of 10 to 14 days.[24,25,92] This response enables the body to cope more effectively with thermal stressors and consists of increases in stroke volume and sweat rate and decreases in heart rate, core body temperature, skin temperature, and sweat salt losses.[17,93,94] Athletes should be allowed to acclimatize to the heat sufficiently before stressful conditions such as full equipment, multiple practices within a day, or performance trials are implemented.[16,23,26,27,88] Individual differences affect the onset and decay of heat acclimatization.[24,25] The rate of acclimatization is related to aerobic conditioning and fitness; in general, a better conditioned athlete will acclimatize to the heat more quickly.

Exercise Intensity. The rate of metabolic heat production is clearly a function of the intensity of physical exertion. The relative intensity of exercise, which is based in part on individual physical fitness, has the greatest influence on the rate of increase in core body temperature.[94] From a physiologic standpoint, high-intensity exercise results in a substantial amount of metabolic heat production, which then produces a rapid rise in core body temperature.[95–97] This rapid rise in temperature often exceeds the ability of the body to dissipate heat, ultimately overwhelming the thermoregulatory system. From a behavioral standpoint, individuals will often use an anticipatory defense mechanism and behavioral modifications (eg, slowing their pace) to protect themselves against dangerous levels of hyperthermia.[98,99] However, during competition, the will to win or to accomplish a personal best may trump this internal cue. In addition, external pressure from coaches or teammates may force athletes to ignore this protective instinct.[54,88]

Overzealousness. Overzealous athletes are at higher risk for EHI because they tend to override the normal behavioral adaptations to heat and ignore early warning signs of EHI.[42,88]

Poor Physical Condition. Untrained individuals are more susceptible to EHI than trained individuals because, as aerobic power ($\dot{V}O_2max$) improves, the ability to withstand heat stress generally also improves.[42,44–46] High-intensity exercise can readily produce 1000 kcal/h and elevate the core temperature of at-risk athletes (those who are unfit, overweight, or unacclimatized) to a dangerous level in less than 30 minutes.[94]

Increased Body Mass Index. Obese people are at increased risk for EHI because they are less efficient in dissipating heat and produce more metabolic heat during exercise. Conversely, those who are muscle bound produce increased metabolic heat and have a lower ratio of surface area to mass, contributing to a decreased ability to dissipate heat.[42,100]

Dehydration. Excess sweat loss, inadequate fluid intake, vomiting, diarrhea, certain medications, and alcohol can lead to a measureable fluid deficit. Proper hydration can help to reduce exercise heart rate,[15,34,101–103] fatigue,[12,104] and core body temperature,[105,106] while improving performance[105–107] and cognitive functioning.[81,108–111] Dehydration of as little as 2% of body weight can negatively affect performance and thermoregulation.[32,34] Caution should be taken to ensure that athletes arrive at practice euhydrated (ie, having reestablished their weight since the last practice) and replace body water that is lost during practice. Measuring body-weight change before, during, and after a practice or an event and across successive days is the preferred method for monitoring dehydration in the field. Using a clinical refractometer is another effective method of estimating hydration status: specific gravity should be no more than 1.020 at the start of the activity.[16,31,32,42] Hydration status can also be identified by monitoring the first-void morning urine color via a urine color chart (urine color should be no more than 4).[31,42]

Water loss that is not sufficiently regained by the next practice increases the risk for EHI.[11,27,31,32] Cumulative dehydration develops insidiously over several days and is typically observed during the first few days of preseason practices[112] and in tournament competition. Cumulative dehydration can be detected by monitoring daily prepractice and postpractice body weights and morning urine color. During intense exercise in the heat, sweat rates can be as high as 2 L/h; if the fluid is not replaced, large deficits will result.[27] Therefore, the rehydration rate may have to be increased during exercise periods of this nature in order to minimize fluid deficits.

Illness. Individuals who are currently or were recently ill may be at increased risk for EHI because of fever, dehydration, or medications (eg, decongestants or antidiarrheal agents).[27,42]

History of Exertional Heat Illness. Athletes with a history of heat illness are often at greater risk for recurrent heat illness during strenuous physical activity due to the potential for widespread debilitation involving the thermoregulatory, central nervous, cardiovascular,

musculoskeletal, renal, and hepatic systems.[20,33,42,65–68] However, these long-term effects are markedly reduced if proper treatment is initiated within 10 minutes of collapse.[57] Identifying the cause of the heat illness and making appropriate decisions to correct the cause will decrease the risk of subsequent heat illnesses.[66] Therefore, the clinician's thorough understanding of the common causes and predisposing factors of EHI is extremely important. Addressing these common causes and implementing proper strategies to mitigate their harmful effects may be the most important approach in avoiding EHIs.

Medications and Drugs. Individuals who take certain medications or drugs, particularly those with a dehydrating effect or those that increase metabolic rate, are at increased risk for EHI.[113–116] Medications that have been suggested to have an adverse effect on thermoregulation include stimulants, antihistamines, anticholinergics, and antipsychotics.[116] Approximately one-third of high school football players reportedly used dietary supplements, most for the purpose of increasing muscle mass.[113] Although such substances do not preclude participation, clinicians should recognize that these athletes are at higher risk and ensure adherence to acclimatization and hydration strategies and observe and intervene to protect if the athlete appears to be struggling.

Electrolyte Imbalance. Electrolyte imbalances can occur even in trained, acclimatized individuals who engage in regular physical activity and eat a normal diet. Most sodium and chloride losses occur through the urine, but people with high sweat rates (eg, >2 L/h) and sodium concentrations and those who are not heat acclimatized can lose significant amounts of sodium during physical activity. It is important to emphasize that athletes' meals should replace electrolyte losses and thereby allow them to avoid salt-depletion dehydration. Electrolyte imbalances also commonly arise with the use of diuretics.[117,118]

Hospitalization and Recovery

After an episode of EHS, the patient may experience impaired thermoregulation, persistent CNS dysfunction, hepatic insufficiency, and renal insufficiency.[65–67,119] For persons with EHS and associated multisystem tissue damage, the rate of recovery is highly individualized, ranging up to more than 1 year.[65,119–121] However, evidence indicates that the degree of morbidity is negatively associated with proper recognition and treatment.[69] If EHS is quickly recognized and immediately treated, morbidity and mortality are significantly decreased.

A patient who experiences EHS may have compromised heat tolerance and heat acclimatization even after physician clearance. Additional heat stress may reduce the patient's ability to train and compete due to impaired cardiovascular and thermoregulatory responses.[65,67] After recovery from EHS, an athlete's physical activity should be restricted and the gradual return to sport individualized by a physician. The patient should be monitored daily by the clinician during exercise. During the return to exercise, the patient may experience some detraining and deconditioning not directly related to the EHS. He or she should be evaluated over time to determine if there has been complete recovery of exercise and heat tolerance.

Certified athletic trainers and other allied health care providers must be able to differentiate EAMCs, heat syncope, heat exhaustion, exertional heat injury, and EHS in order to treat these conditions appropriately in athletes. This position statement outlines the NATA's current recommendations to reduce the incidence, improve the recognition, and optimize the treatment of these heat illnesses in athletes. Education and increased awareness will help to reduce both the frequency and severity of heat illnesses in athletes.

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Joint Consensus Statement

Prevention, Diagnosis, and Treatment of the Overtraining Syndrome: Joint Consensus Statement of the European College of Sport Science and the American College of Sports Medicine

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ABSTRACT

Successful training not only must involve overload but also must avoid the combination of excessive overload plus inadequate recovery. Athletes can experience short-term performance decrement without severe psychological or lasting other negative symptoms. This functional overreaching will eventually lead to an improvement in performance after recovery. When athletes do not sufficiently respect the balance between training and recovery, nonfunctional overreaching (NFOR) can occur. The distinction between NFOR and overtraining syndrome (OTS) is very difficult and will depend on the clinical outcome and exclusion diagnosis. The athlete will often show the same clinical, hormonal, and other signs and symptoms. A keyword in the recognition of OTS might be "prolonged maladaptation" not only of the athlete but also of several biological, neurochemical, and hormonal regulation mechanisms. It is generally thought that symptoms of OTS, such as fatigue, performance decline, and mood disturbances, are more severe than those of NFOR. However, there is no scientific evidence to either confirm or refute this suggestion. One approach to understanding the etiology of OTS involves the exclusion of organic diseases or infections and factors such as dietary caloric restriction (negative energy balance) and insufficient carbohydrate and/or protein intake, iron deficiency, magnesium deficiency, allergies, and others together with identification of initiating events or triggers. In this article, we provide the recent status of possible markers for the detection of OTS. Currently, several markers (hormones, performance tests, psychological tests, and biochemical and immune markers) are used, but none of them meet all the criteria to make their use generally accepted. **Key Words:** OVERTRAINING SYNDROME, OVERREACHING, TRAINING, PERFORMANCE, UNDERPERFORMANCE

The goal in training competitive athletes is to provide training loads that are effective in improving performance. During this process, athletes may go through several stages within a competitive season of periodized training. These phases of training range from insufficient training, during the period between competitive seasons or during active rest and taper, to "overreaching" (OR) and "overtraining" (OT), which includes maladaptations and diminished competitive performance. Literature on "OT" has increased enormously; however, the major difficulty is the lack of common and consistent terminology as well as a gold standard for the diagnosis of OT syndrome (OTS).

In 2006, the European College of Sport Science (ECSS) published its consensus statement on OT (94). We decided to write an update and to ask the American College of Sports Medicine to provide input in this article so that this can be considered as a mutual "consensus statement" of both international organizations. In this "consensus statement," we will present the current state of knowledge on the OTS going through its definition, diagnosis, treatment, and prevention.

DEFINITION

Successful training must involve overload but also must avoid the combination of excessive overload with inadequate recovery. The process of intensifying training is commonly

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used by athletes in an attempt to enhance performance. As a consequence, the athlete may experience acute feelings of fatigue and decreases in performance as a result of a single intense training session or an intense training period. The resultant acute fatigue after an adequate rest period can be followed by a positive adaptation or improvement in performance and is the basis of effective training programs. However, if the balance between appropriate training stress and adequate recovery is disrupted, an abnormal training response may occur and a state of "OR" may develop. Beyond this, the evidence for a supercompensation effect after deliberate periods of intensified training is not abundant.

Many recent articles have referred to the work of Kreider et al. (77) for the definition of OT and OR.

Overreaching—an accumulation of training and/or nontraining stress resulting in *short-term* decrement in performance capacity with or without related physiological and psychological signs and symptoms of maladaptation in which restoration of performance capacity may take from *several days to several weeks*.

Overtraining—an accumulation of training and/or nontraining stress resulting in *long-term* decrement in performance capacity with or without related physiological and psychological signs and symptoms of maladaptation in which restoration of performance capacity may take *several weeks or months*.

As stated by several authors (13,55), these definitions suggest that the difference between OT and OR is the amount of time needed for performance restoration and not the type or duration of training stress or degree of impairment. These definitions also imply that there may be an absence of psychological signs associated with the conditions. Because it is possible to recover from a state of OR within a 2-wk period (54,66,77,132), it may be argued that this condition is a relatively normal and harmless stage of the training process. However, athletes who are in an "overtrained" state may take months or possibly years to completely recover.

The difficulty lies in the subtle difference that might exist between extreme overreached athletes and those having an "OTS." The possibility also exists that these states (OR/OTS) show different defining characteristics and that the OT continuum may be an oversimplification.

To avoid misconception of terminology, we here outline the terms OR, OT, and OTS based on the definitions used by Halson and Jeukendrup (55) and Urhausen and Kindermann (139). In these definitions, "OT" is used as a "verb," a process of intensified training with possible outcomes of short-term OR (functional OR (FOR)), extreme OR (nonfunctional OR (NFOR)), or OTS. By using the expression "syndrome," we emphasize the multifactorial etiology and acknowledge that exercise (training) is not necessarily the sole causative factor of the syndrome.

OR is often used by athletes during a typical training cycle to enhance performance. Intensified training can result in a decline in performance; however, when appropriate periods of recovery are provided, a "*supercompensation*" effect may occur with the athlete exhibiting an enhanced performance compared with baseline levels. This process is often used when going on a "training camp" and will lead to a temporary performance decrement, which is followed by improved performance. In this situation, the physiological responses will compensate the training-related stress (133). This form of short-term "OR" can also be called "FOR." When this "intensified training" continues, the athletes can evolve into a state of extreme OR or "NFOR," which will lead to a stagnation or decrease in performance that will not resume for several weeks or months. However, eventually, these athletes will be able to fully recover after sufficient rest. "NFOR" emphasizes that not only the evolution on the "OT continuum" is "quantitatively" determined (i.e., by the increase in training volume) but also "qualitative" changes occur (e.g., signs and symptoms of psychological distress and/or endocrine disturbances). This is in line with the classical concept of "sympathetic versus parasympathetic OTS" (65) and recent neuroendocrine findings using a double exercise test (95,96).

In Figure 1, the different stages that differentiate normal training from OR (FOR and NFOR) and from OTS are

PROCESS	TRAINING (overload)	INTENSIFIED TRAINING →		
OUTCOME	ACUTE FATIGUE	FUNCTIONAL OR (short-term OR)	NON-FUNCTIONAL OVERREACHING (extreme OR)	OVERTRAINING SYNDROME (OTS)
RECOVERY	Day(s)	Days – weeks	Weeks – months	Months - …
PERFORMANCE	INCREASE	Temporary performance decrement (e.g., training camp)	STAGNATION DECREASE	DECREASE

FIGURE 1—Possible presentation of the different stages of training, OR and OTS.

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presented. Training can be defined as a process of overload that is used to disturb homeostasis, which results in acute fatigue leading to an improvement in performance. When training continues or when athletes deliberately use a short-term period (e.g., training camp) to increase training load, they can experience short-term performance decrement without severe psychological or lasting other negative symptoms. This FOR (or short-term OR) will eventually lead to an improvement in performance after recovery. However, when athletes do not sufficiently respect the balance between training and recovery, NFOR (extreme OR) can occur. At this stage, the first signs and symptoms of prolonged training distress such as performance decrements, psychological disturbance (decreased vigor, increased fatigue), and hormonal disturbances will occur, and the athletes will need weeks or months to recover. Several confounding factors such as inadequate nutrition (energy and/or carbohydrate intake), illness (most commonly, upper respiratory tract infections (URTI)), psychosocial stressors (work, team, coach, and family related), and sleep disorders may be present. At this stage, the distinction between NFOR and OTS is very difficult and will depend on the clinical outcome and exclusion diagnosis. The athlete will often show the same clinical, hormonal, and other signs and symptoms. Therefore, the diagnosis of OTS can often only be made retrospectively when the time course can be overseen. A keyword in the recognition of OTS might be "prolonged maladaptation" not only of the athlete but also of several biological, neurochemical, and hormonal regulation mechanisms.

The borderline between optimal performance and performance impairment due to "OTS" is subtle. This applies especially to physiological and biochemical factors. The apparent vagueness surrounding OTS is further complicated by the fact that the clinical features are varied from one individual to another and are nonspecific, anecdotal, and numerous.

DIAGNOSIS

Although in recent years, the knowledge of central pathological mechanisms of OTS has significantly increased, there is still a strong demand for relevant tools for the early diagnosis of OTS. OTS is characterized by a "sport-specific" decrease in performance together with disturbances in mood state. This underperformance persists despite a period of recovery lasting several weeks or months. Importantly, because there is no diagnostic tool to identify (e.g., rule in) an athlete as experiencing OTS, the solution to the differential diagnosis can only be made by excluding all other possible influences on changes in performance and mood state. Therefore, if no explanation for the observed changes can be found, OTS is diagnosed. Early and unequivocal recognition of OTS is virtually impossible because the only certain sign is a decrease in performance during competition or training. The definitive diagnosis of OTS always requires the exclusion of an organic disease, e.g., endocrinological disorders (thyroid or adrenal gland and diabetes), iron deficiency with anemia, or infectious diseases (including myocarditis, hepatitis, and glandular fever). Other major disorders or feeding behaviors such as anorexia nervosa and bulimia should also be excluded. However, it should be emphasized that many endocrinological and clinical findings due to OR and OTS can mimic other diseases. The borderline between under- and overdiagnosis is very difficult to judge.

In essence, it is generally thought that symptoms of OTS, such as fatigue, performance decline, and mood disturbances, are more severe than those of OR. However, there is no scientific evidence to either confirm or refute this suggestion. Hence, there is no objective evidence that the athlete is indeed experiencing OTS. In addition, in the studies that induced a state of OR, many of the physiological and biochemical responses to the increased training were highly variable, with some measures in some studies demonstrating changes and others remaining unaltered, most likely because conditions and the degree of OR and OTS differ and were not comparably described. This is also probably because the signs and symptoms of OTS are individual and it is not feasible and certainly unethical to excessively train an athlete in such a way that he/she will develop OTS. Therefore, prospective studies are lacking and only few data exist on OTS.

One approach to understanding the etiology of OTS involves the exclusion of organic diseases or infections and factors such as dietary caloric restriction (negative energy balance) and insufficient carbohydrate and/or protein intake, iron deficiency, magnesium deficiency, allergies, and so on together with identification of initiating events or triggers. One of the most certain triggers is a training error resulting in an imbalance between load and recovery. Other possible triggers might be the monotony of training, too many competitions, personal and emotional (psychological) problems, and emotional demands of occupation. Less commonly cited possibilities are sleep disturbance, altitude exposure, and exercise heat stress. However, scientific evidence is not strong for most of these potential triggers. Many triggers such as glycogen deficiency or infections may contribute to OR or OTS but might not be present at the time the athlete presents to a physician. Furthermore, identifying these possible initiating events has not revealed the causative mechanism(s) of the OTS. Consequently, some scientists have suggested that the OTS be renamed as the unexplained underperformance syndrome (13) that focuses on the key symptom of underperformance in OTS rather than on the mechanisms. This terminology has not been widely adopted outside the UK.

Athletes and the field of sports medicine in general would benefit greatly if a specific, sensitive simple diagnostic test existed for the diagnosis of OTS. At present, no test meets this criterion, but there certainly is a need for a combination of diagnostic aids to pinpoint possible markers for OTS. Especially, there is a need for a detection mechanism for early triggering factors.

Increased training loads as well as other chronic stresses can influence the neuroendocrine system chronically. However, at this time, it is not yet clear which mechanism

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eventually leads to OTS. Probably because of this, and because there are several possible hypotheses, some recent review articles have focused on hypothetical explanations for the mechanism behind the OTS. Although these theories have potential, until more prospective studies are carried out where a longitudinal follow-up of athletes (who may develop the OTS) is performed or specific diagnostic tools are developed, these theories remain speculative.

PREVALENCE

It is difficult to give exact prevalence figures on NFOR/OTS merely because not all studies clearly indicate the time frame of data collection. Survey research involving collegiate swimmers and other endurance athletes who completed a training monocycle report a rate of NFOR/OTS of approximately 10% (range, 7%–21%) (118). Higher rates have been reported in other studies, but these values are likely inflated by merging cases of FOR, NFOR, and OTS. The risk of NFOR/OTS becomes compounded over the course of an athlete's career; survey studies of elite runners report 60% of females and 64% of males indicate experiencing at least one previous episode of OTS, with a career rate of 33% in nonelite adult runners (102,103). Similar career rates of OTS have been reported by young athletes, including a 34.6% rate among 231 (age range, 13–18) age-group swimmers from four countries, with OTS being most common among faster performers (117), and a 37% rate in 272 Swedish high school junior national athletes assessed across 16 different sports (72). Retrospective techniques can be prone to bias or inaccurate recall, but a recent longitudinal study of British age-group swimmers found 29% had developed NFOR/OTS at least once, with the risk positively related to skill level (91). These findings reinforce both the growing risk of OTS for young athletes and the utility of retrospective methodologies in OTS research.

Moreover, there is evidence that athletes who have developed OTS are at a heightened risk of relapse. In a study of US collegiate swimmers, it was found that 91% of the swimmers who developed OTS during their first collegiate training season were diagnosed with OTS again in one or more of the following 3 yr of training. In contrast, only 34% of swimmers free of OTS during their first year of collegiate swimming had a later diagnosis of OTS (113).

This interindividual variation in the risk for NFOR/OTS has been observed in athletes who undergo the same overload training. In a study of 13 competitive swimmers who completed 10 d of intensified training at the same volume and relative intensity (8970 $m \cdot d^{-1}$ at 94% $\dot{V}O_{2max}$), seven swimmers successfully completed the required training regimen but three others had difficultly completing the training requirements, and these athletes had significantly higher levels of POMS mood disturbance (101) and lower levels of muscle glycogen (76). Another three swimmers were so severely affected by the training that they had to be dropped from the study.

It remains unclear whether these findings indicate that some individuals are particularly predisposed to developing the OTS when exposed to overload training or whether succumbing to the OTS raises the risk of relapse. Some tests of potential psychological factors have been conducted and have not found the risk of OTS to be mediated by intrinsic motivation (114), hardiness, or optimism (147).

ASSESSMENT OF OT

OTS reflects the attempt of the human body to cope with physiological and other stressors. Several studies have revealed that OTS represents the sum of multiple life stressors, such as physical training, sleep loss, exposure to environmental stresses (e.g., exposure to heat, high humidity, cold, and high altitude), occupational pressures, change of residence, and interpersonal difficulties. Thus, OTS can be understood partly within the context of the General Adaptation Syndrome of Selye (124). Concomitant to this "stress disturbance," the endocrine system is called upon to counteract the stress situation. The primary hormone products (adrenaline, noradrenaline, and cortisol) all serve to redistribute metabolic fuels, maintain blood glucose, and enhance the responsiveness of the cardiovascular system. Repeated exposure to stress may lead to altered responsiveness to subsequent stressful experiences depending on the stressor as well as on the stimuli paired with the stressor, either leading to an unchanged or increased or decreased neurotransmitter and receptor function. Behavioral adaptation (neurotransmitter release, receptor sensitivity, receptor binding, etc.) in higher brain centers will certainly influence hypothalamic output (80). Lehmann et al. (86) introduced the concept that hypothalamic function reflects the state of OR or OTS because the hypothalamus integrates many of the stressors. It has been shown that acute stress increases not only hypothalamic monoamine release but also consequently corticotropin-releasing hormone and adrenocorticotropic hormone (ACTH) secretion (126). Chronic stress and the subsequent chronically elevated adrenal glucocorticoid secretion could play an important role in the desensitization of higher brain centers' response to acute stressors, because it has been shown that in acute and chronic stress, the responsiveness of hypothalamic corticotropin-releasing hormone neurons rapidly falls (6,18,85,137).

The lack of definitive diagnostic criteria for OTS is reflected in much of the "OR" and "OT" research by a lack of consistent findings. There are several criteria that a reliable marker for the onset of the OTS must fulfill: the marker should be sensitive to the training load and ideally be unaffected by other factors (e.g., diet and chronobiological rhythms). Changes in the marker should occur before the establishment of the OTS, and changes in response to acute exercise should be distinguishable from chronic changes. Ideally, the marker should be relatively easy to measure with a quick availability of the result, not too invasive (e.g., repeated venous blood samplings are not well accepted) and

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not too expensive. Ideally, the marker should be derived at rest from submaximal or standardized exercise of relatively short duration in order not to interfere with the training process. However, none of the currently available or suggested markers meet all of these criteria.

BIOCHEMISTRY AND HORMONES

Biochemistry. In prolonged training, glycogen stores get close to full depletion, glycogenolysis and glucose transport are down-regulated in muscle and liver as well as the liver production of insulin-like growth factor 1, and catabolism is induced. Although this is one of the likely triggers of OTS, muscle glycogen is typically normal when athletes are examined (130). Blood glucose is also not typically altered (138). Resting blood glucose/insulin ratio may indicate mild insulin resistance (133).

Blood lactate measurements can be dependent on the actual training status of the individual. Other factors that are equally important when discussing changes in blood lactate concentrations are the glycogen status and possible decreases in muscle and liver stores due to increased training. One almost consistent overall finding, at least in endurance and strength–endurance athletes having the OTS, is a diminished maximal lactate concentration while submaximal values remain unchanged or slightly reduced (139).

Individually increased circulating levels of creatine kinase (CK), which especially reacts to eccentric and unaccustomed exercise with elevations lasting from several days to up to a little over 1 wk, and/or urea measured under standardized conditions at rest (140), may provide information concerning an elevated muscular and/or metabolic strain (137), but they are not suitable to indicate an OR or OTS state (137). Under glycogen-depleted compared with carbohydrate-loaded condition, serum urea increases not only during 1 h of cycling at 61% $\dot{V}O_{2max}$ but also before and 4 h after exercise (88). After one single eccentric strength exercise leading to a nearly 10-fold maximal CK increase with a weak significant correlation to the isometric strength loss, the positive response to concentric strength training was significantly delayed for several weeks (33).

After 2 wk of OR with short-term decline of performance and mood state, plasma CK (as well as glutamate) showed a significant and urea a tendency to increase before normalizing after 2 wk of regenerative training in eight moderately well trained cyclists (57).

The concentration of plasma glutamine has been suggested as a possible indicator of excessive training stress (122). However, not all studies have found a fall during periods of increased training and OT (145), and altered plasma glutamine concentrations are not a causative factor of immunodepression in OTS, whereas other authors rather propose the glutamine/glutamate ratio as an indicator of OR (19,128).

Although most of the blood parameters (e.g., blood count, C-reactive protein, erythrocyte sedimentation rate, CK, urea, creatinine, liver enzymes, glucose, ferritin, sodium, and potassium) are not capable of detecting OR or OTS, they are helpful in providing information on the actual health status of the athlete and therefore useful in the "exclusion diagnosis."

The problems with biochemistry testing are as follows:

- Lactate differences are sometimes subtle (lying within the measuring error of the apparatus) and depend on the modus of the exercise test used.
- No lactate changes are reported in strength athletes.
- Glutamine may fall with increased training load, but low plasma glutamine concentration is not a consistent finding in OTS.

Hormones. For several years, it has been hypothesized that a hormonal mediated central dysregulation occurs during the pathogenesis of the OTS, and that measurements of blood hormones could help to detect the OTS (40,45,79, 85,96,132,133,136,137). The results of the research devoted to this subject is far from unanimous, mostly because of preanalytical factors; i.e., factors that occur before the final analysis (time of sampling, food intake, time after the end of exercise, gender, age, etc.) may influence the hormonal profile. In addition, measuring methods and/or detection limits of the analytical equipment used may differ between studies. Testing of central hypothalamic/pituitary regulation requires functional tests that are considered invasive and require diagnostic experience, and these tests are time consuming and expensive. Finally, the distinguishing characteristic of endocrine systems is the feedback control of hormone production. Virtually all hormones are under feedback control, some by the peripheral hormones themselves, some by other hormones or cytokines, peripheral metabolites, osmolality, etc. This feedback relationship is the reason why simultaneous assessment of hormone/effector pairs is frequently necessary for the assessment of hormonal status, taking also into consideration the fact that physiological processes related to endocrine regulation are influenced by more than a single hormone in a multilevel integrated way (25).

For a long time, the resting plasma testosterone/cortisol ratio was considered as an indicator of the overtrained state. This ratio decreases in relation to the intensity and duration of training, and it is evident that this ratio indicates only the actual physiological strain of training and cannot be used for diagnosis of OR or OTS (25,84,87,136).

Most of the literature agrees that OR and OTS must be viewed on a continuum with a disturbance, an adaptation, and finally a maladaptation of the hypothalamic pituitary adrenal axis (HPA) and all other hypothalamic axes (85,87,93, 96,136,138). For example, the HPA adaptation to normal training is characterized by increased ACTH/cortisol ratio only during exercise recovery (due to decreased pituitary sensitivity to cortisol) (26,27,85) and by modulation of tissue sensitivity to glucocorticoids (28,30). However, it should be emphasized that during a resting day, in endurance-trained athletes, 24 h of cortisol secretion under nonexercising conditions is normal (28,30,82). Accordingly, morning plasma

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cortisol concentration and 24-h urinary free cortisol excretion in resting endurance-trained men are similar to those of age-matched sedentary subjects (29,53,74). Because urinary free cortisol represents an integrated measure of the 24-h cortisol secretion, this is in accordance with the previously reported normal diurnal HPA axis rhythm in endurance-trained men (28,29). Finally, endurance-trained men maintain the seasonal rhythmicity of cortisol excretion; as in sedentary men, the highest concentrations of urinary cortisol, morning plasma cortisol, and saliva cortisol are observed during autumn and winter compared with spring and summer (53). Therefore, it can be concluded that resting cortisol is not a useful measurement.

There is no consensus about plasma, 24-h, or overnight urinary excretion of catecholamines for monitoring the effect of the training load and/or an overload. Some studies report an increase, a decrease, or no change of urinary catecholamine excretion (for a review see Duclos [25]) with successful training, OR or OTS. Factors other than training load influence secretion and could result in variations between studies; these factors include sampling methods, diurnal and seasonal variations of catecholamine excretion, and sex difference effects. Because the relationship between 24 h or nocturnal catecholamine urinary excretion and performance or training monitoring is inconclusive, it is thus inappropriate to use changes in catecholamine excretion as a tool to monitor training status.

In OTS, a decreased rise in pituitary hormones (ACTH, growth hormone (GH), luteinizing hormone, and FSH) in response to a stressful stimulus is reported (6,85,136, 137,148). But behind the seemingly uniform acute hormonal response to exercise, explaining the disturbance to the neuroendocrine system caused by the OTS is not that simple. Whether peripheral metabolic hormones can be used for OR/OTS diagnosis is currently under discussion.

A nutrient-sensing signal of adipose tissue is represented by leptin (127), which, like the glucoregulatory hormone insulin, interleukin-6, and metabolic growth factor insulin-like growth factor 1, has been shown to decrease with training-induced catabolism like in OR. These signaling molecules have profound effects on the hypothalamus and are involved in the metabolic hormonal regulation of exercise and training (133). However, the same molecules respond to chronic energy deficiency, which can be associated with endurance training and/or aesthetic sports (e.g., gymnastics), regardless of the training status (absence or presence of OR/OTS). Chronic energy deficiency (mainly glycogen depletion) certainly amplifies the stress hormone and cytokine responses to exercise and might also be one of the "triggering" factors that can lead to the induction of OTS.

In addition to the need to study different hormonal axes in parallel, it is also important to consider the dynamics of hormonal responses. Indeed, the hormonal responses during exercise influence the hormonal responses during exercise recovery (24,29,68), and it is therefore important to study both phases of exercise. For this reason, a multiple exercise test that not only gives the opportunity to measure the recovery capacity of the athlete but also can assess the ability to normally perform the second bout of exercise could be useful to detect signs of OTS and distinguish them from normal training responses or FOR.

Meeusen et al. (96) published a test protocol with two consecutive maximal exercise tests separated by 4 h. The use of two bouts of incremental exercise to volitional exhaustion to study neuroendocrine variations showed an exercise-induced increase of ACTH, prolactin, and GH to a two-exercise bout (96). In normal healthy subjects, the test reveals an increase in the circulating concentrations of the hormones after both the first and the second exercise bout. The test could be used as an indirect measure of hypothalamic–pituitary reactivity. Depending on the "training" status of the athlete, hormonal output after the second exercise test will be different. This test has the ability to distinguish a state of NFOR from the OTS. In an FOR stage, a less pronounced neuroendocrine response to a second bout of exercise on the same day is found (96), whereas in an NFOR stage, the hormonal response to a two-bout exercise protocol shows a markedly higher elevation after the second exercise trigger (96). With the same protocol, it has been shown that athletes experiencing OTS have an extremely large increase in circulating hormone concentration after the first exercise bout, followed by a complete suppression in the second exercise bout (95,96). This could indicate a hypersensitivity of the pituitary followed by an insensitivity or exhaustion afterward. Previous reports that used a single-exercise protocol found similar effects (96). In a follow-up study, they could clearly distinguish between NFO and OTS athletes (95). It appears that the use of two-exercise bouts is more useful in detecting OR for preventing OT. Early detection of OR may be very important in the prevention of OTS.

Other hormones such as leptin, adiponectin, and ghrelin, as well as cytokines such as interleukin-6 and tumor necrosis factor-alpha, have been recently investigated as possibilities for the monitoring of training (67). The authors concluded that although some of these parameters measured in the fasting state or postexercise may provide information about energetic regulatory mechanisms and may change after heavy training or inadequate recovery, there are no studies supporting the possible suitability of these variables as markers of training stress or for the prevention or diagnosis of OR or OTS.

In conclusion, the endocrine system is one of the major systems involved in the responses to acute stress and adaptation to chronic stress. A great diversity of mechanisms is involved in such adaptation, acting at potentially all levels in the cascade, leading to the biological effects of the hormones. However, the current information regarding the endocrine system and OR/OTS shows that basal (resting) hormone measurements cannot distinguish between athletes who successfully adapt to OR and those who fail to adapt

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and develop symptoms of OTS. Further studies using multiple exercise tests and/or multiple hormone analyses will be necessary for evaluating the possibility of a hormonal diagnostic test for OR/OTS.

The problems with hormonal data are as follows:

- Many factors affect blood hormone concentrations, and these include factors linked to sampling conditions and/or conservation of the sampling: stress of the sampling, intra- and interassay coefficient of variability;
- Food intake (nutrient composition and/or pre- vs postmeal sampling) can modify significantly either the basal concentration of some hormones (cortisol, Dehydroepiandrosteron-sulphate, and total testosterone) or their concentration change in response to exercise (cortisol and GH);
- Pulsatility of the secretion of some hormones, which modulates the tissue sensitivity to these hormones;
- In female athletes, the hormonal response will depend on the phase of the menstrual cycle;
- Aerobic and resistance protocols typically elicit different endocrine responses;
- Hormone concentrations at rest and after stimulation (exercise = acute stimulus) respond differently;
- Diurnal and seasonal variations of the hormones;
- Stress-induced measures (exercise, pro-hormones, etc) need to be compared with baseline measures from the same individual;
- Poor reproducibility and feasibility of some techniques used to measure some hormones (e.g., free testosterone by radio immunoassay instead of the reference method—reserved to some highly specialized centers—equilibrium dialysis);
- Hormonal responses to exercise can be prolonged during the recovery phase of exercise.

PERFORMANCE TESTING

In athletes who have been diagnosed as having OTS, several signs and symptoms have been associated with this imbalance between training and recovery. However, reliable diagnostic markers for distinguishing between well-trained athletes, OR athletes, and athletes having OTS are lacking. A hallmark feature of OTS is the inability to sustain intense exercise, a decreased sport-specific performance capacity when the training load is maintained or even increased (96,136). Athletes experiencing OTS are usually able to start a normal training sequence or a race at their normal training pace but are not able to complete the training load they are given, or race as usual. The key indicator of OTS can be considered an unexplainable decrease in performance. Therefore, an exercise/performance test is considered to be essential for the diagnosis of OTS (13,136).

It appears that both the type of performance test used and the intensity/duration of the test are important in determining the changes in performance associated with OTS. Debate exists as to which performance test is the most appropriate when attempting to diagnose OR and OTS. In general, time-to-fatigue tests will most likely show greater changes in exercise capacity as a result of OR and OTS than incremental exercise tests (55,138). Time trials reflect more accurately the sport-specific task of most sports but have only rarely been used to objectively quantify the performance loss in OR (57). In addition, these tests allow that the assessment of substrate kinetics, hormonal responses, and submaximal measures can be made at a fixed intensity and duration. To detect subtle performance decrements, it might be better to use sport-specific performance tests. Tests of high-intensity exercise performance may be appropriate in some sports. For example, isokinetic strength and power were shown to be decreased in seven overreached rugby players (20) but increased after 1 wk of taper.

The problems with performance testing are as follows:

- Baseline measures are often not available, and therefore, the degree of performance limitation may not be exactly determined. Individual comparative values are mandatory.
- The intensity and reproducibility of the test should be sufficient to detect differences (maximum test, time trial).
- Necessity of highly standardized conditions from one test to another and from one laboratory to another.
- Many performance tests are not sport specific.
- Submaximal ergometric test results do not seem to produce significant results (137), but repeated maximal tests, required for assessment of an individual baseline measure, are difficult to obtain in athletes.
- In this regard, because adequate standardization of laboratory tests is problematic, it may be that index training sessions recorded by coaches are better candidates to demonstrate the magnitude, timing, and pattern of performance decrements.

PSYCHOLOGY

The presence of psychological symptoms in cases of OTS has long been acknowledged (22), but systematic study on this topic did not begin until William Morgan's research in the 1980s on college swimmers and athletes in other sports. Using the POMS (100), a questionnaire that measures both general and specific moods, athletes were found to consistently report elevations in negative moods (tension, depression, anger, fatigue, and confusion) and decreases in the positive mood of vigor during periods of rigorous training. More frequent assessments indicated that mood state exhibits a predictable dose–response relationship with training whereby disturbances increase in a stepwise fashion as training loads rise in volume or intensity, with the peak of training and mood disturbance coinciding. Conversely, training tapers usually result in a reduction in negative moods and an increase in vigor such that at the end of a taper, the mood scores return to the positive pattern typically observed at the outset of the season, called the iceberg profile (100,103,116). Dose–response relationships between training

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load and mood state have since been observed in studies involving more than 1000 athletes in a variety of endurance and nonendurance sports requiring rigorous training regimens (118).

Research also indicates that mood responses of male and female athletes do not differ except when they are exposed to significantly different training regimens (103,115). Similar dose–response patterns have also been observed using simple self-report measures of muscle soreness, appetite, sleep disturbances, "heaviness," and perception of effort (72,101,110,118), indicating perceptual responses to increased training are global and systemic in nature, although the magnitude of change differs across measures (102,118).

When conditioning programs involve rapid increases in training load over a course of days, the instructions to complete psychological measures should, if possible, be modified to yield a more transient state measure of mood by having subjects respond according to how they feel "today" or "right now." Research reveals that as few as 2 d of intensified training can result in significant increases in POMS measures (110) and scores on other psychological scales, which precede changes in commonly used biochemical markers of training stress such as cortisol (19,111). More important for the standpoint of monitoring, athletes with signs of OTS typically exhibit both a greater increase in total mood disturbance and a different pattern of mood disturbance compared with athletes undergoing the same training who remain free from symptoms (114). Specifically, among healthy athletes, POMS fatigue and vigor show the largest shifts during peak overload training, and depression increases the least of all POMS factors, whereas in athletes showing signs of OTS, depression increases the most of all POMS variables, with some reports (103) indicating that up to 80% of affected athletes show signs of clinical depression. As shown in Figure 2, mood changes between healthy and overtrained athletes.

The previous findings have led to tests of mood state monitoring as a means to modulate training load with the goal of reducing the incidence of OTS. This intervention paradigm involved reducing the training load of athletes possessing excessively elevated POMS total mood disturbance scores until scores fell within an acceptable range established *a priori* using either off-season baseline of each athlete (7) or the mean value for teammates undergoing the same training regimen (113). Conversely, training loads were increased in athletes exhibiting only minor mood disturbances, and this intervention was nearly as frequent as cases in which training loads were reduced (7). Both studies reported a reduced incidence of OTS compared with previous rates, but replications incorporating involving larger samples and adequate control conditions remain needed.

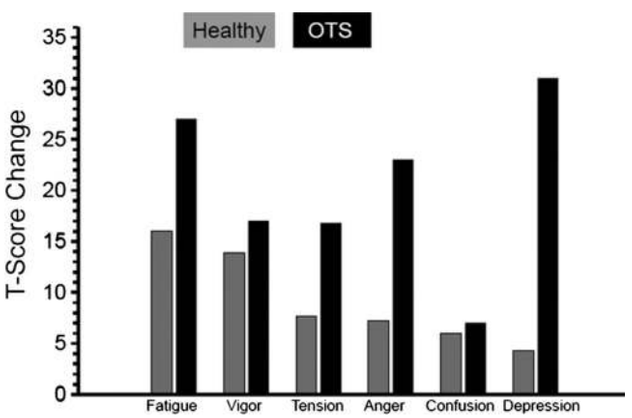

FIGURE 2—Magnitude of changes in POMS mood states from easy to maximal overload training in collegiate varsity swimmers who develop OTS or remain free of symptoms (i.e., "healthy"). (Adapted from Raglin and Morgan [114]).

Although research generally supports the use of psychological assessments for identifying individuals at risk of developing OTS, several potential problems exist that can constrain accuracy. The most serious among these is response distortion, wherein subjects falsely complete psychological questionnaires, particularly those with items of a sensitive or personal nature. The most common form of response distortion involves social desirability or "faking good" in which individuals answer items to present themselves in a uniformly positive light. Factors that can increase the likelihood of response distortion include coercion, the demand characteristics associated with the experimental hypothesis, or in the case of OT studies, "faking bad" to have one's training load reduced. Administering questionnaires repeatedly over an extended period can sometimes result in a form of response distortion in which participants respond to questions in a random manner. The risk of response distortion can be reduced by including research team members who are trained in the proper administration of psychological questionnaires, providing athletes clear and guaranteed assurances their data will remain confidential and not be used for selection purposes, and by carefully explaining the rationale of using psychological assessments while emphasizing there are no right or wrong ways to respond to the questionnaires.

A separate concern regarding the POMS is the finding that the sensitivity of the mood subscales to training load is not uniform. Some factors, particularly confusion, barely change even after large increases in training load in either healthy or overtrained athletes, whereas other POMS subscales are responsive to non–training-related sport stressors (116). For example, POMS tension scores often remain elevated or even increase during training tapers, most likely because this factor is particularly sensitive to the impending stress of major competitions (116). At a more fundamental level, the POMS was designed for use in general circumstances and samples, and many sport psychologists contend that sport-specific questionnaires should provide greater sensitivity and specificity for assessing athletes in the unique environment of sport. Consequently, several hundred sport-specific psychological measures of personality, motivation, and mood have been developed, including several for NFOR/OTS. In the case of OTS, the decision to use a general or sport-specific measure depends not only on published

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evidence of its predictive efficacy and construct validity but also the theoretical orientation of the researcher. If it is believed the risk of OTS is a function of the sum total of stressors an athlete is exposed to—be they training related or not—then a nonspecific questionnaire that captures broad moods, feelings, or perceptions would be most appropriate. Conversely, if non–sport-related stressors (e.g., psychosocial stressors and time zone travel) are viewed as inconsequential or only minor contributors to the OTS, then questionnaires delimited to items particular to the context of training should be used.

For these and other reasons, researchers have developed POMS-based OT scales in the attempt to enhance its sensitivity. Raglin and Morgan (114) created a Training Distress Scale (TDS) based on discriminant function analyses of POMS data from 186 healthy and overtrained college swimmers. A TDS spreadsheet may be accessed at http://champ.usuhs.mil/choptimize.html. The seven-item (five depression and two anger items) TDS was more accurate in identifying OT athletes compared with predictions using POMS total mood disturbance scores or depression scores, and subsequent research (72,118) using translations of the scale in several languages found TDS scores to be elevated in young swimmers reporting OTS. Kenttä et al. (73) created a POMS energy index measure by subtracting fatigue from vigor scores to study 11 elite kayakers during an intensive 3-wk training camp. The researchers had athletes complete the entire POMS after practice each day and in the morning before practice to assess mood state after training and recovery. POMS energy index scores were responsive to both training stress and recovery, whereas depression scores were unchanged, suggesting to the authors the index could be a useful tool to reduce NFOR during intense but brief training cycles.

Several sport-specific OTS scales have been developed using theoretical assumptions about what psychological and behavior factors should be associated with OTS. Among them, the most extensively studied has been the Recovery–Stress Questionnaire for Athletes (RESTQ-Sport) (70), a 77-item questionnaire encompassing 19 separate factors that assess both OT and recovery responses in endurance athletes. Monitoring the current levels both of stress and recovery has the possible advantage that problems may be detected before symptoms of OT and staleness (e.g., drowsiness, apathy, fatigue, and irritability) are likely to appear. However, stress and recovery are often different in their time course. Although concerns with its factor structure have been expressed by other researchers (e.g., Ref. [23]), research indicates the RESTQ is responsive to changes in training load, particularly in athletes with signs of OTS (69). Other less well-documented OTS scales include the questionnaire of the Société Francaise de Médicine du Sport (SFMS), a 54-item forced-choice (i.e., yes–no) questionnaire that assesses whether athletes have experienced mood disturbances and various symptoms of OT during the previous month (cited in Ref. [31]), and the Daily Analyses of Life-Demands in Athletes, a 50-item scale with two sections assessing general and sport-related stresses (123) experienced over the past day using a three-point Likert format.

In summary, research has provided general support for the efficacy of psychological assessments in both basic and applied research involving athletes undergoing overload training. There remains, however, a need for systematic study of the relative efficacy (i.e., sensitivity and specificity) of promising measures and tests to establish protocols that effectively integrate psychological information with biological assessments to enhance their efficacy.

Psychomotor speed tests. A relatively new but promising tool in the early detection of NFO and therefore a potential preventive tool in developing an OTS is the measurement of psychomotor speed. The advantage of psychomotor speed testing above most other tests lays in the fact that it is easy to use in the (sport) field just by using a simple personal computer. The tests are noninvasive, resistant to conscious manipulation by the athlete, and inexpensive.

It is well described that symptoms such as concentration and memory problems and cognitive complaints are common in patients experiencing chronic fatigue syndrome (45), symptoms also found in people experiencing OTS (85,125). These similarities have led to the use of attention and reaction time tests for early detection of NFO and preventing OTS. Rietjens et al. (120) used a reaction time test (finger precuing test) as a detection tool for NFO. They found a significant decrease in reaction time in a group of seven cyclists after they had doubled their training volume over a period of 3 wk (120), especially on the more difficult conditions in the finger precuing reaction time task, with the more easy conditions being insensitive to OR. This outcome suggests that task complexity is an important mediating variable in the relationship between OR and brain functioning. In line with these findings Nederhof et al. (104) described a decrease in reaction time in five NFO cyclists after a 2-wk training camp. In a later follow-up study, Nederhof et al. (105,106) confirmed these findings.

More recently, Hynynen et al. (64) presented data in which OTS cyclists scored a significantly higher number of mistakes during a STROOP test. All these studies strongly suggest that central fatigue is an early (and maybe the most early) manifestation of OR. This suggestion is ratified by the findings of Tergau et al. (134) who found an intracortical facilitation increase after exercise, indicating motor cortex fatigue.

These findings indicate that reaction and attention tests are promising tools in early detection of NFO and preventing OTS. However, more scientific studies are needed to find out which kind of psychomotor speed tests are the most sensitive for detecting NFO/OTS.

The potential problems with psychological assessments are as follows:

- Mood state and other factors can be influenced by stressors unrelated to training and recovery.

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- It remains unclear if intervention paradigms based on psychological information should use off-season baseline mood scores (i.e., intraindividual criterion), team averages (i.e., interindividual) or combinations of baseline and training values would be more effective.
- Psychological measures can be biased or rendered invalid by various forms of faking (e.g., social desirability) or overuse.
- Psychological tests must be administered with the appropriate instructional set (e.g., "right now," "today," and "last week including today") based on the training paradigm. Care must be taken with state (i.e., "right now") measures of mood because they can be influenced by extraneous factors.
- Care needs to be taken to explain the potential value of psychological measures to coaches and athletes who may be reluctant or skeptical. Researchers should be trained in the administration and interpretation of the measures used.

PHYSIOLOGY

There have been several proposals as to which physiological measures might be indicative of OR or OTS. Reduced maximal heart rates after increased training may be the result of reduced sympathetic nervous system activity, of a decreased tissue responsiveness to catecholamines, and of changes in adrenergic receptor activity or may simply be the result of a reduced power output achieved with maximal effort. Several other reductions in maximal physiological measures (oxygen uptake, heart rate, blood lactate) might be a consequence of a reduction in exercise time and not related to abnormalities *per se*, and it should be noted that changes of resting heart rate are not consistently found in athletes experiencing OTS (139).

Heart rate variability (HRV) analysis has been used as a measure of cardiac autonomic balance, with an increase in HRV indicating an increase in vagal (parasympathetic) tone relative to sympathetic activity (143). Numerous studies have examined the effects of training on indices of HRV, but to date, few studies have investigated HRV in overreached or OTS athletes, with studies showing either no change (3,58,142), inconsistent changes (143), or changes in parasympathetic modulation (59).

Hedelin et al. (58) increased the training load of nine canoeists by 50% over a 6-d training camp. Running time to fatigue, $\dot{V}O_{2max}$, submaximal and maximal heart rates, and maximal blood lactate production all decreased in response to the intensified training; however, all indices of HRV remained unchanged. On average, there were no significant changes in low-frequency power, high-frequency power, total power, or the ratio of low- to high-frequency power, both in the supine position and after head-up tilt. Similarly, Uusitalo et al. (142) reported no change in intrinsic heart rate and autonomic balance in female athletes after 6–9 wk of intensified training. This involved the investigation of autonomic balance assessed by pharmacological vagal and β-blockade. In addition, both the time domain and power spectral analysis in the frequency domain were calculated during rest and in response to head-up tilt. Results suggest that HRV in the upright position had a tendency to decrease in response to intensified training in the subjects who were identified as "overtrained" (143). This may indicate vagal withdrawal and/or increased sympathetic activity. However, between-subject variability was high in this investigation. Finally, Hedelin et al. (58) reported increased HRV and decreased resting heart rate in a single "overtrained" athlete when compared with baseline measures. In comparison with normally responding subjects examined during the same period, the "overtrained" subject exhibited an increase in high frequency and total power in the supine position during intensified training, which decreased after recovery. The increase in high-frequency power was suggested to be most likely the result of increased parasympathetic activity (59).

Lamberts et al. (81) proposed that the heart rate return 1 min after high intensity interval exercise could serve to monitor training because it showed some correlation with the evolution of time trial performance after 4 wk in 14 moderately well-trained cyclists, but to date, there are no published results available from athletes in OR or OTS.

In a very recent study (12) in young soccer players, a decrease of submaximal heart rate, a faster return of heart rate after exercise, and an increase of vagal indices of HRV were associated with some positive adaptations to training, but the opposite was not true because "negative" changes of theses markers were not indicators of a performance decline.

A meta-analysis (10) concluded that short-term (<2 wk) overload training results in an increased resting heart rate (mean value, +4.5 bpm), decreased maximal heart rate (−7.5 bpm), and a higher ratio between low- and high-frequency HRV. However, this was no longer the case after longer intensified training interventions lasting >2 wk, where the only significant difference remained a decreased maximal heart rate (−3.6 bpm).

Concerning the assumption often claimed in a clinical context that cardiac complications such as arrhythmias or other ECG changes discovered in athletes could be explained by a state of OR or OTS, this hypothesis does not find any support by any study inducing OR or OTS. However, it should be mentioned that an infectious disease—maybe facilitated by the intermittently depressed immunological state—occurring in an athlete engaged in heavy training may expose the individual to a higher risk of cardiac complications including a higher heart rate, extrasystoles, and even myocarditis (38).

The problems with physiological measures are as follows:

- HRV seems to be a tool in theory but does not provide consistent results. One needs to be careful when using HRV as an outcome measure because there are many different ways to record and calculate the data. Currently, there is no consensus regarding the required standardization and the method of measurement.

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- The present data do not allow to distinguish between changes in physiological measures resulting from FOR, NFOR, and OTS.

IMMUNE SYSTEM

There are many reports on URTI due to increased training, and also in OR and OTS athletes. It seems feasible that intensified training (leading to OR or OTS) may increase both the duration of the so-called "open window" and the degree of the resultant immunodepression. However, the amount of scientific information to substantiate these arguments is limited. More data are available that each bout of prolonged and intensive exercise has transient but significant, wide ranging effects on the immune system (49,108). Heavy exertion leads to alterations in immunity and host pathogen defense and elevations in stress hormones, pro- and anti-inflammatory cytokines, and reactive oxygen species. The exercise-induced immune perturbations and physiologic stress are associated with an elevated risk of URTI, especially during the 1- 2-wk period after competitive marathon and ultramarathon race events (109). These data imply that chronic immune dysfunction and increased URTI symptomatology may result when exercise training is intensified, leading to OR and OTS, but few well-designed studies have been conducted to verify this hypothesis.

Several studies that have investigated the effects of short periods (typically 1–3 wk) of intensified training on resting immune function and on immunoendocrine responses to endurance exercise indicate that several indices of neutrophil function appear to be sensitive to the training load. A 2-wk period of intensified training in well-trained triathletes was associated with a 20% fall in the bacterially stimulated neutrophil degranulation response (121). In another study, neutrophil and monocyte oxidative burst activity, mitogen-stimulated lymphocyte proliferation, and percentage and number of T-cells producing interferon-γ were lower at rest after 1 wk of intensified training in cyclists (83). Other leukocyte functions including T-lymphocyte $CD4^+/CD8^+$ ratios, lymphocyte antibody synthesis, and natural killer cell cytotoxic activity have been shown to be lower after increases in the training load in already well-trained athletes (144). Several studies have documented a fall in salivary immunoglobulin A (IgA) concentration with intensified training, and some, although not all, have observed a negative relationship between salivary IgA concentration and occurrence of URTI (9,32,47,50,107). Thus, with sustained periods of heavy training, several aspects of both innate and adaptive immunity are depressed. Low levels of salivary IgA concentration or secretion rate and high anti-inflammatory cytokine responses to antigen challenge may predispose to high respiratory illness susceptibility in athletes (32,47,50). Several studies have examined changes in immune function during intensive periods of military training (16,17,135). However, this often involves not only strenuous physical activity but also dietary energy deficiency, sleep deprivation, and psychological challenges. These multiple stressors are likely to induce a pattern of immunoendocrine responses that amplify the exercise-induced alterations.

Studies that have examined athletes exposed to a long-term training periods (e.g., over the course of a 5- to 10-month competitive season) have shown a general trend of depression of both systemic and mucosal immunity (5,14,47,48,51,52,99). In these studies, depressed immunity was most commonly observed either at the end of the season or after the most intensive periods of training and/or competition. Although elite athletes are not clinically immune deficient, it is possible that the combined effects of small changes in several immune parameters may compromise resistance to common minor illnesses such as URTI. Protracted immune depression linked with prolonged training may determine susceptibility to infection, particularly at times of major competitions. However, it might just be that the increased URTI incidence reflects the increased stress associated with increased training, regardless of the response of the athlete to the increased physical stress. Furthermore, symptoms of respiratory illness reported by some athletes may be due to airway inflammation from noninfectious causes (8,21,146) rather than actual infection with a pathogen.

Whether that immune function is seriously impaired in athletes experiencing OTS is unknown because of insufficient scientific data. However, anecdotal reports from athletes and coaches of an increased infection rate with OTS (129) have been supported by a few empirical studies (75,119). In a cohort study of highly trained athletes before the Olympic Games, more than 50% of the athletes who reported symptoms of "OT" presented with infection compared with none of the athletes in the overreached group (75). In junior rowers, studied during and after a training camp (FOR), 40% of the male subjects had URTI (132). In a study by Reid et al. (119), 41 competitive athletes with persistent fatigue and impaired performance had a thorough medical examination, which identified medical conditions with the potential to cause fatigue and/or recurrent infections in 68% of the athletes. The most common conditions were humoral immune deficiency and unresolved viral infections. Evidence of Epstein–Barr virus reactivation was detected in 22% of the athletes tested. Adventure racing over a 4- to 5-d period has been linked to significant mood state disruption and elevated URTI rates (4). Thus, it seems plausible that a significant number of athletes who are diagnosed as experiencing OTS may experience increased URTI.

There are only a few reports of differences in immune function status in "overtrained" athletes compared with healthy trained athletes (e.g., Refs. [46,89]), and most studies on "overtrained" athletes have failed to find any differences (90,122). Circulating numbers of lymphocyte subsets change with exercise and training. With heavy training, the T-lymphocyte $CD4^+/CD8^+$ (helper/suppressor) ratio falls. However, this has not been shown to be different in athletes diagnosed as experiencing OTS compared with healthy well-trained athletes. One study (46) has shown that the expression of other proteins

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on the cell surface of T-lymphocytes does seem to be sensitive enough to distinguish between the majority of "overtrained" athletes and healthy athletes. The expression of CD45RO on T-helper $CD4^+$ cells (but not the circulating numbers of $CD45RO^+$ T-cells) was significantly higher in athletes experiencing OTS compared with healthy well-trained controls. Using this indicator, "OT" could be classified with high specificity and sensitivity. However, CD45RO is a marker of T-memory cells and activated T-cells. Thus, higher expression of CD45RO on T-cells may merely be indicative of the presence of acute infection, which is, of course, a possible cause of the underperformance. Fry et al. (44) reported a significant increase in activation markers [CD25, human leucocyte antigen receptor test (HLA-DR)] in blood lymphocytes of "overtrained" athletes. Unresolved viral infections are not routinely assessed in elite athletes, but it may be worth investigating this in individuals experiencing fatigue and underperformance in training and competition. Thus, infection might be one of the "triggering" factors that can lead to the induction of OTS, or in some cases, the diagnosis of OTS cannot be differentiated from a state of postviral fatigue such as that observed with episodes of glandular fever. In the OTS diagnostic flowchart (Fig. 3), it is recommended to evaluate for "primary" viral and bacterial infections and systemic inflammatory diseases before proceeding with the diagnostic workup in direction OTS. It is acknowledged in the flowchart that, secondary in the time course of OTS, a reactivation of Epstein–Barr virus can be detected (119), which may contribute to the severity of symptoms. However, despite that this distinction between "primary" and "secondary" infection may be in some cases clinically difficult, it may help in the explanation and treatment of fatigue and underperformance-related diseases.

In conclusion, it is clear that the immune system is sensitive to stress—both physiological and psychological—and thus, potentially, immune variables could be used as an index of stress in relation to exercise training. The current information regarding the immune system and OR confirms that periods of intensified training result in depressed immune cell functions with little or no alteration in circulating cell numbers. However, although immune parameters change in response to increased training load, these changes do not distinguish between those athletes who successfully adapt to OR and those who maladapt and develop symptoms of the OTS. Furthermore, at present, it seems that measures of immune function cannot really distinguish OTS from infection or postviral fatigue states.

The problems with immunological testing are as follows:

- timing of the test (time of the day and time since last exercise session),
- lack of consistency of the data in literature,
- being time consuming and very expensive (for functional measures).

Resistance exercise. Although most research on OT and OR has focused on endurance activities, some research has shed light on stressful training when using heavy resistance exercise, and it is summarized in several reviews (39,40,42,43). What has become clear is that excessively high volumes or intensities of resistance exercise can present considerably different physiological and performance profiles when compared with OT/OR with endurance activities. When excessive volumes of maximal loads are used for training, maximal muscular strength is one of the last performance measures to be adversely affected. On the other hand, high speed (e.g., sprinting) and power appear to be more sensitive to the stressful resistance exercise training and are the first types of performance to decrease. Although not greatly studied, some data also indicate that psychological variables may be sensitive to resistance exercise OT/OR. From an endocrine perspective, although testosterone concentrations and the testosterone/cortisol ratio may decrease because of resistance exercise OT/OR, these cannot be used to define the presence of an OTS. Rather, these hormonal measures simply indicate the presence of stressful training. When resistance-trained athletes are exposed to a repeated stressful training phase, the decreased hormonal response is lessened, suggesting that repeated training of this type may permit long-term training tolerance. The presence of an elevated acute sympathetic response with excessive resistance exercise loads supports the concept of a sympathetic OTS. This in turn may contribute to down-regulation of β_2 adrenergic receptors in the affected skeletal muscle (41). From a practical standpoint, the actual training program must be carefully monitored to incorporate adequate recovery phases as needed. Finally, it is readily apparent that sport-specific training in addition to the resistance exercise program can add to the training stresses and contribute to OT/OR (98).

The problems with resistance exercise OT/OR research are as follows:

- There are few research studies on resistance exercise OT/OR.
- There are many variations of resistance exercise that make it difficult to study.
- Muscular strength is usually preserved with resistance exercise OT/OR.
- Delayed onset muscular soreness and muscle damage are not necessarily the same as resistance exercise OT/OR.
- Few studies have monitored an adequate recovery period.

Prevention. One general confounding factor when reviewing literature on OTS is that the definition and diagnosis of OR and OTS are not standardized. One can even question if in most of the studies subjects were experiencing OTS. Because OTS is difficult to diagnose, authors agree that it is important to prevent OTS (37,78,141). Moreover, because OTS is mainly due to an imbalance in the training recovery ratio (too much training and competitions and too little recovery), it is of utmost importance that athletes record daily their training load, using a daily training diary or

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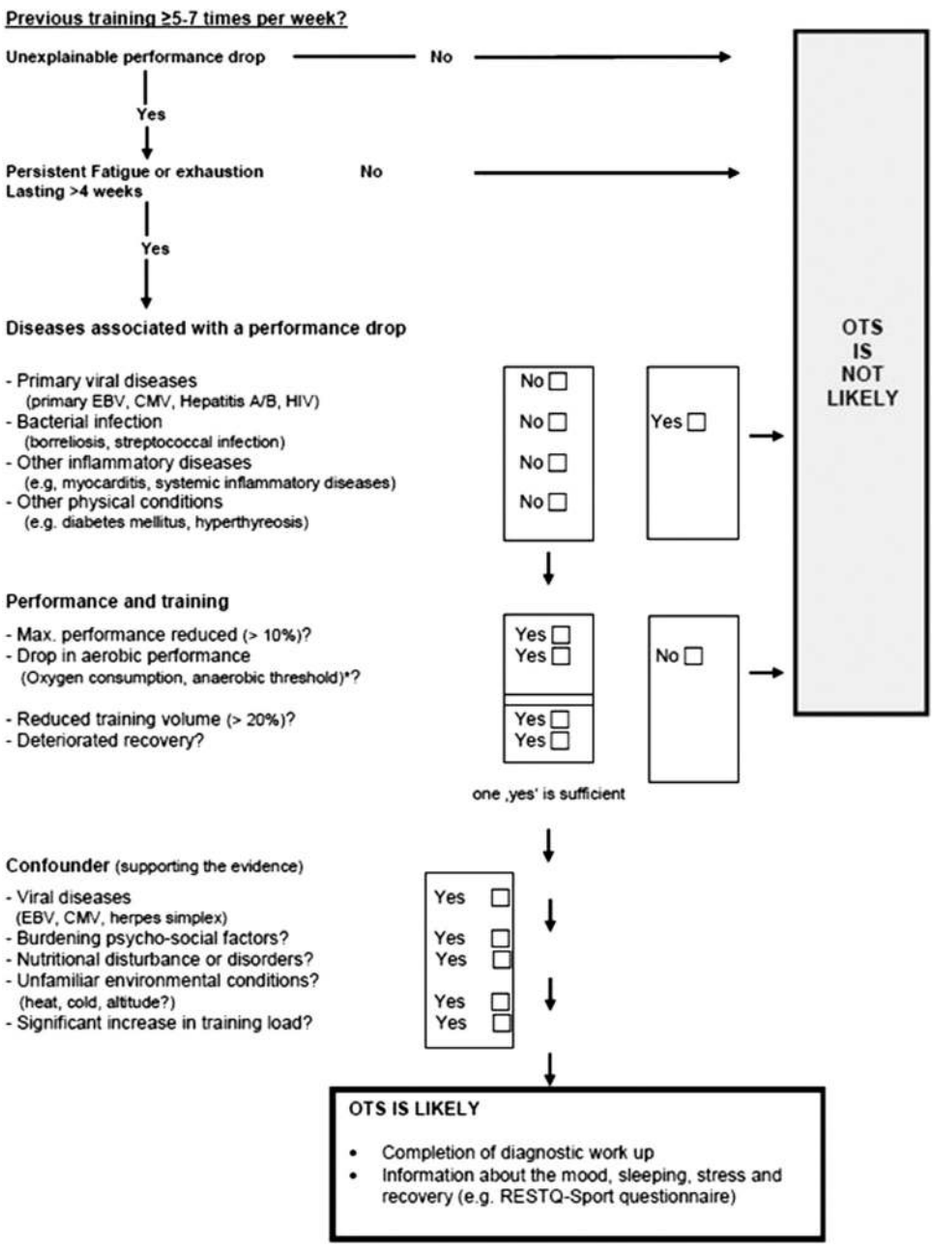

FIGURE 3—Flowchart. Diagnosis of OTS in athletes. When previous training load was high enough, the occurrence of persistent problems in performance creates a suspicion for OTS. The flowchart starts with the key symptoms: decrease in performance; duration of symptoms; then other major diseases that are related to underperformance are ruled out; then performance changes are defined and then possible confounding conditions and diseases are checked. This flowchart is based on the existing evidence together with the expertise/experience of the authors.

training log (34,35,37). The four methods most frequently used to monitor training and prevent OT are as follows: retrospective questionnaires, training diaries, physiological screening, and the direct observational method (62). Also, the psychological screening of athletes (7,60,61,92,101,102, 116,138) and the RPE (1,15,34,35,60,61,71,131) have received more and more attention nowadays.

Hooper et al. (61) used daily training logs during an entire season in swimmers to detect staleness (OTS). The distances swum, the dry-land work time, and the subjective self-assessment of training intensity were recorded. In addition to these training details, the swimmers also recorded subjective ratings of quality of sleep, fatigue, stress and muscle soreness, body mass, early morning heart rate, occurrence of illness, menstruation, and causes of stress. Swimmers were classified as having OTS if their profile met five criteria. Three of these criteria were determined by items of the daily training logs: fatigue ratings in the logs of more than 5 (scale 1–7) lasting longer than 7 d, comments in the page provided in each log that the athlete was feeling that

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he/she responded poorly to training, and a negative response to a question regarding presence of illness in the swimmer's log, together with normal blood leukocyte count.

Foster et al. (35,37) have determined training load as the product of the subjective intensity of a training session using "session RPE" and the total duration of the training session expressed in minutes. If these parameters are summated on a weekly basis, it is called the total training load of an individual. The "session RPE" has been shown to be related to the average percent heart rate reserve during an exercise session and to the percentage of a training session during which the heart rate is in blood lactate–derived heart rate training zones. With this method of monitoring training, they have demonstrated the utility of evaluating experimental alterations in training and have successfully related training load to its performance (35). Foster et al. (36) have demonstrated that athletes often do not perform the same training load prescribed by coaches. In particular, they noted that on days the coaches intended to be "easy," athletes often performed meaningfully longer and/or more intense training. These data fit well with the concept that OTS is a failure of the work–recovery relationship, often in the direction of athletes failing to take appropriate recovery. However, training load is clearly not the only training-related variable contributing to the genesis of OTS. So additional to the weekly training load, daily mean training load as well as the SD of training load was calculated during each week. The daily mean divided by the SD was defined as the monotony. The product of the weekly training load and monotony was calculated as strain. The incidence of simple illness and injury was noted and plotted together with the indices of training load, monotony, and strain. They noted the correspondence between spikes in the indices of training monotony and strain and subsequent illness or injury and thresholds that allowed for optimal explanation of illnesses were computed (34). The data in this study (34) were suggested by earlier data by Bruin et al. (11) in race horses. The horses responded appropriately to progressive increases in the training load until the normal recovery days were made harder (e.g., the monotony of training was increased). At this point, the running performance of the horses deteriorated and the horses demonstrated behavioral signs consistent with an equine version of OTS (e.g., being "off their feed," which included loss of appetite, biting their handlers and kicking their stalls). This finding of a sudden deterioration of performance with loss of normal regeneration is also consistent with the differences in training program design by coaches versus execution by athletes (36).

One of the disadvantages of the traditional "paper and pencil" method is that data collection can be complicated, and that immediate feedback is not always possible. Another problem is that when athletes are on an international training camp or competition, immediate "data computing" is not possible. It might therefore be useful to have an "online" training log that has specific features in detecting not only slight differences in training load but also the subjective parameters (muscle soreness and mental and physical well-being) that have been proven to be important in the detection of OTS.

Strategies to reduce the symptoms of OR and reduce the risk of developing OTS. Both in the earlier data, reviewed in the ECSS 2006 consensus statement, and in the more contemporary data in this document, there is virtually no evidence suggesting that OTS can be "treated." Like a massive orthopedic injury, OTS (and even NFOR) is just as debilitating and takes a substantial time for recovery to occur spontaneously. Rest and very light training seem to be the only therapeutic agents capable of effecting recovery. The overwhelming impression, particularly in the evidence that has emerged since 2006, is that the emphasis needs to be on prevention of NFOR and OTS (mostly by appropriate periodization of the training program with careful focus on including, and executing, appropriate recovery time into the training program) and on early diagnosis of NFOR and OTS, which at least in principle might shorten the recovery time.

Rest and sleep. One of the most obvious methods for managing fatigue and enhancing recovery is adequate passive rest and obtaining sufficient sleep. It is generally recommended that athletes should have at least one passive rest day each week, because the absence of a recovery day, especially during intensified training periods, is closely related to the onset of signs of OR and underrecovery (11). A passive rest day can also act as a "time-out" period for athletes and prevent them from becoming totally preoccupied with their sport and possibly encourage them to pursue a different (passive) interest. Such distractions from the daily routine of training may alleviate boredom and reduce stress perception.

Sleep is an essential part of fatigue management, because persistent sleep loss can negatively affect the quality of a training session and general well-being. The primary need for sleep has been hypothesized as being neurally based rather than a requirement for restitution of other biological tissues (63). Therefore, with inadequate sleep, cognitive functions are likely to be impaired, especially the ability to concentrate. Individuals have different requirements for sleep, and to prescribe the dose of sleep that a highly trained athlete requires would be erroneous. The general advice is to sleep for the amount of time that is required to feel wakeful during the day, which may vary considerably between individuals.

Nutrition. Because OR is brought about by high-intensity training with limited recovery, it is thought that the fatigue and underperformance associated with OR are at least partly attributable to a decrease in muscle glycogen levels. Decreased glycogen levels can result in disturbances of the endocrine milieu. Glycogen depletion results in higher circulating levels of catecholamines, cortisol, and glucagon in response to exercise while insulin levels are very low. Such hormonal responses will result in changes in substrate mobilization and utilization (for instance, high adrenaline levels in combination with low insulin will increase lipolysis and stimulate the mobilization of fatty acids). Because repeated

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days of hard training and carbohydrate depletion seem to be linked to the development of OR, it is tempting to think that carbohydrate supplementation can reverse the symptoms (130). In a group of runners who ran 16 to 21 km on a daily basis for 7 d and treated all those runs as races, performance dropped significantly when a moderate carbohydrate intake of 5.5 $g \cdot kg^{-1}$ body mass per day was maintained (2). The runners also displayed a range of symptoms indicating that they were overreached. But when the daily carbohydrate was increased to 8.5 $g \cdot kg^{-1}$ body mass per day, the drops in performance were much smaller and OR symptoms were reduced. Recovery from this week of hard training was more complete with the high-carbohydrate treatment. In this study, the dietary intake was strictly controlled and the subjects were fed to maintain energy balance. In a follow-up study, subjects received carbohydrate supplements before, during, and after training sessions, but their dietary intake the rest of the day was recorded but not controlled (56). In this study, a group of well-trained cyclists were required to perform 8 d of intensive endurance training (normal training volume was doubled). This training was performed on two occasions separated by a washout, or recovery, period of at least 2 wk. On one occasion, subjects consumed a 2% carbohydrate solution before, during, and after training (low CHO), and on the other occasion, subjects consumed a 6.4% carbohydrate solution before and during training and a 20% carbohydrate solution after training (high CHO). Total carbohydrate intake was 6.4 $g \cdot kg^{-1}$ body mass per day with low CHO and 9.4 $g \cdot kg^{-1}$ body mass per day with high CHO. The intensified training protocol induced OR as indicated by a decrease in performance (time to fatigue at approximately 74% of aerobic capacity), although the decrease in performance was significantly less with high CHO, suggesting that high-CHO diets can reduce the severity of OR. Alteration of mood state (assessed by POMS questionnaire) and hormonal disturbances in the response to exercise were also less on high CHO compared with low CHO. By requiring the subjects to consume supplements that contained a large amount of carbohydrate, the total energy intake increased as well (13.0 vs 16.5 $MJ \cdot d^{-1}$ for low CHO and high CHO, respectively). Athletes in hard training seem to reduce (or not increase) their spontaneous food intake, and unless they supplement with carbohydrate, they may be in negative energy balance during periods of intensified training. It also appeared that the amount of carbohydrate ingested during training influenced the length of time needed for recovery. After 2 wk of recovery (reduced volume and intensity) from intensified training, performance remained below that of baseline for the low-CHO treatment, whereas performance improved compared with baseline after 2 wk of recovery from intensified training with the high-CHO condition.

Besides carbohydrate depletion, dehydration and negative energy balance can increase the stress response (increased catecholamines, cortisol, and glucagon, whereas insulin levels are reduced), which increases the risk of developing OR symptoms. Thus, to reduce the symptoms of OR and reduce the risk of developing OTS during periods of intensive training, athletes should be encouraged to increase their fluid, carbohydrate, and energy intake to meet the increased demands. Additional carbohydrate should not be at the expense of reduced protein intake because there is some evidence that insufficient protein can also result in increased risk of OR (75). Supplementation with amino acids (glutamine and branched chain amino acids), however, is not likely to reduce symptoms of fatigue and OR (97).

Considerations for coaches and physicians. Until a definitive diagnostic tool for the OTS is present, coaches and physicians need to rely on performance decrements as verification that an OTS exists. However, if sophisticated laboratory techniques are not available, the following considerations may be useful:

- Maintain accurate records of performance during training and competition. Be willing to adjust daily training intensity/volume or allow a day of complete rest, when performance declines, or the athlete complains of excessive fatigue.
- Avoid excessive monotony of training.
- Always individualize the intensity of training.
- Encourage and regularly reinforce optimal nutrition, hydration status, and sleep.
- Be aware that multiple stressors such as sleep loss or sleep disturbance (e.g., jet lag), exposure to environmental stressors, occupational pressures, change of residence, and interpersonal or family difficulties may add to the stress of physical training.
- Treat OTS with rest. Reduced training may be sufficient for recovery in some cases of OR.
- Resumption of training should be individualized on the basis of the signs and symptoms because there is no definitive indicator of recovery.
- Communication with the athletes (maybe through an online training diary) about their physical, mental, and emotional concerns is important.
- Include regular psychological questionnaires to evaluate the emotional and psychological state of the athlete.
- Maintain confidentiality regarding each athlete's condition (physical, clinical and mental).
- Importance of regular health checks performed by a multidisciplinary team (physician, nutritionist, psychologist, etc.).
- Allow the athlete time to recover after illness/injury.
- Note the occurrence of URTI and other infectious episodes; the athlete should be encouraged to suspend training or reduce the training intensity when experiencing an infection.
- Always rule out an organic disease in cases of performance decrement.
- Unresolved viral infections are not routinely assessed in elite athletes, but it may be worth investigating this in individuals experiencing fatigue and underperformance in training and competition.

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Moreover, when OTS is suspected, it is also of utmost importance to standardize the criteria used for diagnosis and/or, at least, as tools for the diagnosis of OTS are lacking, to standardize the criteria of exclusion of OTS (see Fig. 1 for the definition and Tables 1 and 2).

CONCLUSION

A difficulty with recognizing and conducting research into athletes with OTS is defining the point at which OTS develops. Many studies claim to have induced OTS, but it is more likely that they have induced a state of OR in their subjects. Consequently, the majority of studies aimed at identifying markers of ensuing OTS are actually reporting markers of excessive exercise stress resulting in the acute condition of OR and not the chronic condition of OTS. The mechanism of OTS could be difficult to examine in detail maybe because the stress caused by excessive training load, in combination with other stressors, might trigger different "defence mechanisms" such as the immunological, neuroendocrine, and other physiological systems that all interact and probably therefore cannot be pinpointed as the "sole" cause of OTS. It might be that as in other syndromes (e.g., chronic fatigue syndrome or burnout), the psychoneuroimmunology (study of brain–behavior–immune interrelationships) might shed a light on the possible mechanisms of OTS, but until there is no definite diagnostic tool, it is of utmost importance to standardize measures that are now thought to provide a good inventory of the training status of the athlete. A primary indicator of OR or OTS is a decrease in sport-specific performance, and it is very important to emphasize the need to distinguish OTS from OR and other potential causes of temporary underperformance such as anemia, acute infection, muscle damage, and insufficient carbohydrate intake.

The physical demands of intensified training are not the only elements in the development of OTS. It seems that a complex set of psychological factors are important in the development of OTS, including excessive expectations from a coach or family members, competitive stress, personality structure, social environment, relationships with family and friends, monotony in training, personal or emotional problems, and school- or work- related demands. Although no single marker can be taken as an indicator of impending OTS, the regular monitoring of a combination of performance, physiological, biochemical, immunological, and psychological variables would seem to be the best strategy to identify athletes who are failing to cope with the stress of training. We therefore propose a "check list" that might help the physicians to decide on the diagnosis of OTS and to exclude other possible causes of underperformance (Table 2).

TABLE 1. Diagnosis of OTS—checklist.

Performance - Fatigue
Is the athlete experiencing the following:
Unexplainable underperformance
Persistent fatigue
Increased sense of effort in training
Sleep disorders
…
Exclusion criteria
Are there confounding diseases?
Anemia
Epstein–Barr virus
Other infectious diseases
Muscle damage (high CK)
Lyme disease
Endocrinological diseases (diabetes, thyroid, adrenal gland, …)
Major disorders of eating behavior
Biological abnormalities (increased erythrocyte sedimentation rate, C-reactive protein, creatinine, or liver enzymes, decreased ferritin, …)
Injury (musculoskeletal system)
Cardiological symptoms
Adult-onset asthma
Allergies
…
Are there training errors?
Training volume increased (>5%) ($h \cdot wk^{-1}$, $km \cdot wk^{-1}$)
Training intensity increased significantly
Training monotony present
High number of competitions
In endurance athletes : decreased performance at "anaerobic" threshold
Exposure to environmental stressors (altitude, heat, cold, …)
…
Other confounding factors:
Psychological signs and symptoms (disturbed POMS, RESTQ-Sport, RPE, …)
Social factors (family, relationships, financial, work, coach, team, …)
Recent or multiple time zone travel
…
Exercise test
Are there baseline values to compare with? (performance, heart rate, hormonal, lactate, …)
Maximal exercise test performance
Submaximal or sport-specific test performance
Multiple performance tests
…

TABLE 2. Methodological prerequisites for studies of markers for NFOR/OTS.

1. Inclusion of a sufficient number of well-trained subjects
2. Definition of a range of meaningful differences by determination of individual ranges of normal variations including phases of FOR
3. Inclusion of measures showing the decline of sport-specific performance ("gold standard")
4. Exclusion of medical causes (illnesses) of impaired performance
5. Inclusion of markers measured at rest and/or at submaximal exercise
6. Follow-up after a sufficient duration of recovery before final testing

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CURRENT OPINION

International Recommendations for Electrocardiographic Interpretation in Athletes

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ABSTRACT

Sudden cardiac death (SCD) is the leading cause of mortality in athletes during sport. A variety of mostly hereditary, structural, or electrical cardiac disorders are associated with SCD in young athletes, the majority of which can be identified or suggested by abnormalities on a resting 12-lead electrocardiogram (ECG). Whether used for diagnostic or screening purposes, physicians responsible for the cardiovascular care of athletes should be knowledgeable and competent in ECG interpretation in athletes. However, in most countries a shortage of physician expertise limits wider application of the ECG in the care of the athlete. A critical need exists for physician education in modern ECG interpretation that distinguishes normal physiological adaptations in athletes from distinctly abnormal findings suggestive of underlying pathology. Since the original 2010 European Society of Cardiology recommendations for ECG interpretation in athletes, ECG standards have evolved quickly over the last decade; pushed by a growing body of scientific data that both tests proposed criteria sets and establishes new evidence to guide refinements. On February 26-27, 2015, an international group of experts in sports cardiology, inherited cardiac disease, and sports medicine convened in Seattle, Washington, to update contemporary standards for ECG interpretation in athletes. The objective of the meeting was to define and revise ECG interpretation standards based on new and emerging research and to develop a clear guide to the proper evaluation of ECG abnormalities in athletes. This statement represents an international consensus for ECG interpretation in athletes and provides expert opinion-based recommendations linking specific ECG abnormalities and the secondary evaluation for conditions associated with SCD. (J Am Coll Cardiol 2017;69:1057-75) © 2017 The Authors. Published by Elsevier Inc. on behalf of American College of Cardiology Foundation. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

AV = atrioventricular

BrS = Brugada syndrome

DCM = dilated cardiomyopathy

ECG = electrocardiogram

HCM = hypertrophic cardiomyopathy

IVCD = intra-ventricular conduction delay

LBBB = left bundle branch block

LGE = late gadolinium enhancement

LQTS = long QT syndrome

LVH = left ventricular hypertrophy

LVNC = left ventricular noncompaction

MRI = magnetic resonance imaging

RBBB = right bundle branch block

RVH = right ventricular hypertrophy

SAECG = signal average electrocardiogram

SCD = sudden cardiac death

SVT = supraventricular tachycardia

TWI = T-wave inversion

VF = ventricular fibrillation

VPC = ventricular premature contractions

WPW = Wolf-Parkinson-White

INTRODUCTION

Cardiovascular-related sudden death is the leading cause of mortality in athletes during sport and exercise (1–3). The majority of disorders associated with an increased risk of sudden cardiac death (SCD) are suggested or identified by abnormalities on a resting 12-lead ECG. Whether used for the evaluation of cardiovascular-related symptoms, a family history of inheritable cardiac disease or premature SCD, or for screening of asymptomatic athletes, ECG interpretation is an essential skill for all physicians involved in the cardiovascular care of athletes.

THE 2015 SUMMIT ON ECG INTERPRETATION IN ATHLETES. Over the last decade, ECG interpretation standards have undergone several modifications to improve the accuracy of detecting potentially life threatening cardiac conditions in young athletes while also limiting false positive results (4–15). In February 2015, an international group of experts convened in Seattle, Washington, to update contemporary recommendations for ECG interpretation in asymptomatic athletes age 12 to 35 years. The goals of the summit meeting were to: 1) update ECG interpretation standards based on new and emerging research; and 2) develop a clear guide to the appropriate evaluation of ECG abnormalities for conditions associated with SCD in athletes. In the presence of cardiac symptoms or a family history of inherited cardiovascular disease or premature SCD, a normal ECG should not preclude further assessment.

This document provides the most updated evidence-based recommendations developed with thoughtful attention to balance sensitivity and specificity, while maintaining a clear and practical checklist of findings to guide ECG interpretation for physicians and the appropriate evaluation of ECG abnormalities. A summary of the consensus recommendations is presented in **Figure 1** and **Tables 1 and 2**.

LIMITATIONS. While ECG increases the ability to detect underlying cardiovascular conditions associated with SCD, ECG as a diagnostic tool has limitations in both sensitivity and specificity. Specifically, ECG is unable to detect anomalous coronary arteries, premature coronary atherosclerosis, and aortopathies. In some instances patients with cardiomyopathies, particularly arrhythmogenic right ventricular cardiomyopathy (ARVC), may also reveal a normal ECG. Thus, an ECG will not detect all conditions predisposing to SCD. Furthermore, inter-observer variability among physicians remains a major concern (16–18), despite studies demonstrating that using standardized criteria improves interpretation accuracy (19,20).

NORMAL ECG FINDINGS IN ATHLETES

PHYSIOLOGICAL CARDIAC ADAPTATIONS TO REGULAR EXERCISE. Regular and long-term participation in intensive exercise (minimum of 4 h per week) is associated with unique electrical manifestations that reflect enlarged cardiac chamber size and increased vagal tone. These ECG findings in athletes are considered normal, physiological adaptations to regular exercise and do not require further evaluation (**Figure 1**, **Table 1**).

LEFT AND RIGHT VENTRICULAR HYPERTROPHY. The presence of isolated QRS voltage criterion for left ventricular hypertrophy (LVH) (**Figure 2**) does not correlate with pathology in athletes and is present in isolation (without other associated ECG abnormalities) in <2% of patients with hypertrophic

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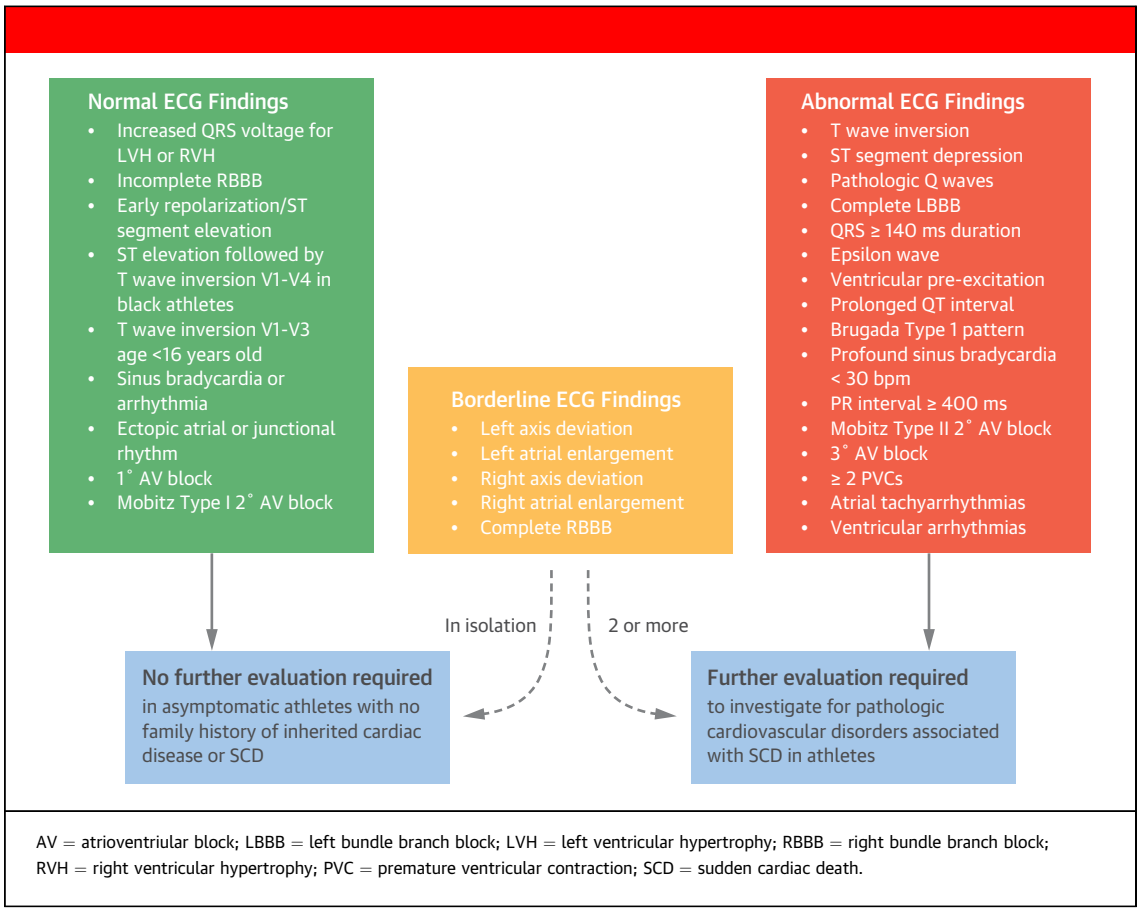
*The first 2 authors contributed equally to the study.



AV = atrioventriular block; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; PVC = premature ventricular contraction; SCD = sudden cardiac death.

cardiomyopathy (HCM) (21-27). Conversely, pathological LVH is commonly associated with additional ECG features such as T-wave inversion (TWI) in the inferior and lateral leads, ST-segment depression, and pathological Q waves (28,29). Therefore, the isolated presence of high QRS voltages fulfilling voltage criterion for LVH in the absence of other ECG or clinical markers suggestive of pathology are considered part of normal and training-related ECG changes in athletes and does not require further evaluation.

Voltage criterion for right ventricular hypertrophy (RVH) is also common in athletes with up to 13% of athletes fulfilling the Sokolow-Lyon index (30,31). QRS voltages for RVH, when present in isolation, do not correlate with underlying pathology in athletes (31). Similar to voltage criteria for LVH, isolated QRS voltage for RVH is part of the normal spectrum of ECG findings in athletes and does not require further evaluation.

EARLY REPOLARIZATION. Early repolarization is defined as elevation of the QRS-ST junction (J-point) by ≥ 0.1 mV often associated with a late QRS slurring or notching (J-wave) affecting the inferior and/or lateral leads (32–34). Early repolarization is common in healthy populations (2% to 44%) and is more prevalent in athletes, young individuals, males, and black ethnicity (32,35–39). Early repolarization consisting of J-point elevation with concave ST-segment elevation and a peaked TWI (**Figure 2**) is present in up to 45% of Caucasian athletes and 63% to 91% of black athletes of African-Caribbean descent (hereto referred to as 'black' athletes) (22,30).

Some studies on survivors of cardiac arrest and patients with primary ventricular fibrillation (VF) have suggested an association between early repolarization and the risk of VF (33,40). Although further studies are warranted to fully elucidate the mechanisms and prognostic implications of early repolarization in competitive athletes, to date there are no data to support an association between inferior early repolarization and SCD in athletes. Based on current evidence, all patterns of early repolarization, when present in isolation and without clinical markers of pathology, should be considered benign variants in athletes (41).

REPOLARIZATION FINDINGS IN BLACK ATHLETES. Ethnicity is a major determinant of cardiac adaptation to exercise with more than two-thirds of black athletes exhibiting repolarization changes (29,30,42,43). Black athletes also commonly demonstrate a repolarization

Abnormal ECG findings in athletes
These ECG findings are unrelated to regular training or expected physiologic adaptation to exercise, may suggest the presence of pathologic cardiovascular disease, and require further diagnostic investigation.

ECG abnormality	Definition
T wave inversion	≥1 mm in depth in two or more contiguous leads; excludes leads aVR, III, and V_1
Anterior	V_2–V_4
	– excludes: black athletes with J-point elevation and convex ST-segment elevation followed by TWI in V_2–V_4; athletes age <16 with TWI in V_1–V_3; and biphasic T waves in only V_3
Lateral	I and AVL, V_5 and/or V_6 (only one lead of TWI required in V_5 or V_6)
Inferolateral	II and aVF, V_5–V_6, I and AVL
Inferior	II and aVF
ST-segment depression	≥0.5 mm in depth in two or more contiguous leads
Pathologic Q waves	Q/R ratio ≥0.25 or ≥40 ms in duration in two or more leads (excluding III and aVR)
Complete left bundle branch block	QRS ≥120 ms, predominantly negative QRS complex in lead V_1 (QS or rS), and upright notched or slurred R wave in leads I and V_6
Profound nonspecific intra-ventricular conduction delay	Any QRS duration ≥140 ms
Epsilon wave	Distinct low amplitude signal (small positive deflection or notch) between the end of the QRS complex and onset of the T-wave in leads V_1–V_3
Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (≥120 ms)
Prolonged QT interval*	QTc ≥470 ms (male)
	QTc ≥480 ms (female)
	QTc ≥500 ms (marked QT prolongation)
Brugada Type 1 pattern	Coved pattern: initial ST-segment elevation ≥2 mm (high take-off) with downsloping ST-segment elevation followed by a negative symmetric T-wave in ≥ 1 leads in V_1–V_3
Profound sinus bradycardia	<30 beats/min or sinus pauses ≥3 s
Profound 1° AV block	≥400 ms
Mobitz Type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval
3° AV block	Complete heart block
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter
PVC	≥2 PVCs per 10 s tracing
Ventricular arrhythmias	Couplets, triplets, and non-sustained ventricular tachycardia

Borderline ECG findings in athletes
These ECG findings in isolation likely do not represent pathologic cardiovascular disease in athletes, but the presence of two or more borderline findings may warrant additional investigation until further data become available.

ECG abnormality	Definition
Left axis deviation	−30° to −90°
Left atrial enlargement	Prolonged P wave duration of >120 ms in leads I or II with negative portion of the P-wave ≥1 mm in depth and ≥40 ms in duration in lead V_1
Right axis deviation	>120°
Right atrial enlargement	P-wave ≥2.5 mm in II, III, or aVF
Complete right bundle branch block	rSR′ pattern in lead V1 and a S wave wider than R wave in lead V_6 with QRS duration ≥120 ms

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variant consisting of J-point elevation and convex ST-segment elevation in the anterior leads (V_1 to V_4) followed by TWI (**Figures 3, 4B, and 4C**) which is regarded as a normal variant and should not result in further investigation, in the absence of other clinical or ECG features of cardiomyopathy (30,42–44).

CONSIDERATIONS IN ATHLETES AGE 12 TO 16 YEARS: THE 'JUVENILE' ELECTROCARDIOGRAM PATTERN. TWI confined to the anterior precordial leads may be considered a normal age-related pattern in adolescent athletes up to the age of 16 years old. The term 'juvenile' ECG pattern is used to denote TWI or a biphasic T-wave beyond lead V_2 in adolescents who have not reached physical maturity and is present in 10%–15% of white, adolescent athletes aged 12 years old but only in 2.5% of white athletes age 14 to 15 years (**Figure 4A**) (22,45,46). Anterior TWI that extends beyond lead V_2 is rare (0.1%) in white athletes age ≥16 years or younger athletes who have completed puberty (22,45). Based on current evidence, TWI in the anterior leads (V_1 to V_3) in adolescent athletes <16 years of age should not prompt further evaluation in the absence of symptoms, signs, or a family history of cardiac disease.

PHYSIOLOGICAL ARRHYTHMIAS IN ATHLETES. Common consequences of increased vagal tone include sinus bradycardia and sinus arrhythmia (22,47–49). Other, less common markers of increased vagal tone are

Normal ECG findings in athletes

These training-related ECG alterations are physiologic adaptations to regular exercise, considered normal variants in athletes, and do not require further evaluation in asymptomatic athletes with no significant family history.

Normal ECG finding	Definition
Increased QRS voltage	Isolated QRS voltage criteria for left (SV1 + RV5 or RV6 >3.5 mV) or right ventricular hypertrophy (RV1 + SV5 or SV6 >1.1 mV)
Incomplete RBBB	rSR′ pattern in lead V_1 and a qRS pattern in lead V_6 with QRS duration <120 ms
Early repolarization	J-point elevation, ST-segment elevation, J waves, or terminal QRS slurring in the inferior and/or lateral leads
Black athlete repolarization variant	J-point elevation and convex ('domed') ST-segment elevation followed by T-wave inversion in leads V_1–V_4 in black athletes
Juvenile T-wave pattern	T-wave inversion V_1–V_3 in athletes age <16 yrs
Sinus bradycardia	≥30 beats/min
Sinus arrhythmia	Heart rate variation with respiration: rate increases during inspiration and decreases during expiration
Ectopic atrial rhythm	P waves are a different morphology compared with the sinus P-wave, such as negative P waves in the inferior leads ('low atrial rhythm')
Junctional escape rhythm	QRS rate is faster than the resting P-wave or sinus rate and typically <100 beats/min with narrow QRS complex unless the baseline QRS is conducted with aberrancy
1° AV block	PR interval 200–400 ms
Mobitz Type I (Wenckebach) 2° AV block	PR interval progressively lengthens until there is a non-conducted P-wave with no QRS complex; the first PR interval after the dropped beat is shorter than the last conducted PR interval

*The QT interval corrected for heart rate is ideally measured using Bazett's formula with heart rates between 60 and 90 beats/min; preferably performed manually in lead II or V_5 using the teach-the-tangent method[1] to avoid inclusion of a U-wave (please see text for more details). Consider repeating the ECG after mild aerobic activity for a heart rate <50 beats/min, or repeating the ECG after a longer resting period for a heart rate >100 beats/min, if the QTc value is borderline or abnormal.

AV = atrioventricular block; ECG = electrocardiogram; PVC = premature ventricular contraction; RBBB = right bundle branch block.

junctional or ectopic atrial rhythms, first degree atrioventricular (AV) block, and Mobitz Type I second degree AV block (Wenckebach phenomenon) (22,47,50). In the absence of symptoms, heart rates ≥ 30 beats/min are considered normal in highly trained athletes. Sinus rhythm should resume and bradycardia should resolve with the onset of physical activity.

BORDERLINE ELECTROCARDIOGRAM FINDINGS IN ATHLETES

Recent data suggest that some ECG findings previously categorized as abnormal may represent normal variants or the result of physiological cardiac remodeling in athletes and do not usually represent pathological cardiac disease. These ECG findings have been categorized as 'borderline' findings in athletes (**Figure 1**, **Table 1**).

AXIS DEVIATION AND VOLTAGE CRITERIA FOR ATRIAL ENLARGEMENT. Axis deviation and voltage criteria for atrial enlargement account for >40% of abnormal ECG patterns in athletes but do not correlate with cardiac pathology (51). In a large study of 2,533 athletes age 14 to 35 years old and 9,997 controls of similar age, echocardiographic evaluation of the 579 athletes and controls with isolated axis deviation or voltage criteria for atrial enlargement failed to identify any major structural or functional abnormalities (51).

COMPLETE RIGHT BUNDLE BRANCH BLOCK. Although incomplete right bundle branch block (RBBB) is common in young athletes, the significance of complete RBBB is less certain. Complete RBBB is detected in approximately 1% of the general population and large datasets in young adult athletes reveal a prevalence of 0.5% to 2.5% (12,52–54). In a study of 510 U.S. collegiate athletes, RBBB was reported in 2.5% and compared with athletes with normal QRS complexes or incomplete RBBB, athletes with complete RBBB exhibited larger right ventricular dimensions and a lower right ventricular ejection fraction but preserved fractional area change (55). None of the athletes with complete RBBB or incomplete RBBB was found to have pathological structural cardiac disease. These patterns among trained athletes could represent a spectrum of structural and physiological cardiac remodeling characterized by RV dilation with resultant QRS prolongation and a relative reduction in the RV systolic function at rest (55).

Based on the aforementioned considerations, left axis deviation, left atrial enlargement, right axis deviation and right atrial enlargement and complete RBBB are considered borderline variants in athletes. The presence of any one of these findings in isolation or with other recognized physiological electrical patterns of athletic training does not warrant further assessment in asymptomatic athletes without a family history of premature cardiac disease or SCD. Conversely, the presence of more than one of these borderline findings places the athlete in the abnormal category warranting additional investigation.

ECG Abnormality	Potential Cardiac Disease*	Recommended Evaluation†	Considerations
T-wave inversion in the lateral or inferolateral leads	HCM DCM LVNC ARVC (with predominant LV involvement) Myocarditis	Echocardiography CMR Exercise ECG test Minimum 24 h ECG monitor	Lateral or inferolateral T wave inversion is common in primary myocardial disease. CMR should be a routine diagnostic test for this ECG phenotype and is superior to echocardiography for detecting apical HCM, LVH localized to the free lateral wall, ARVC with predominant left ventricular involvement, and myocarditis. If CMR is not available, echocardiography with contrast should be considered as an alternative investigation for apical HCM in patients with deep T wave inversion in leads V_5–V_6. Consider family evaluation if available and genetic screening. Annual follow-up testing is recommended throughout athletic career in athletes with normal results.
T-wave inversion isolated to the inferior leads	HCM DCM LVNC Myocarditis	Echocardiography	Consider CMR based on echocardiography findings or clinical suspicion.
T-wave inversion in the anterior leads‡	ARVC DCM	Echocardiography CMR Exercise ECG test Minimum 24 h ECG monitor SAECG	The extent of investigations may vary based on clinical suspicion for ARVC and results from initial testing.
ST-segment depression	HCM DCM LVNC ARVC Myocarditis	Echocardiography	Consider CMR and additional testing based on echocardiography findings or clinical suspicion.
Pathologic Q waves	HCM DCM LVNC Myocarditis Prior MI	Echocardiography CAD risk factor assessment Repeat ECG for septal (V_1–V_2) QS pattern; above investigations recommended if septal Q waves are persistent	Consider CMR (with perfusion study if available) based on echocardiography findings or clinical suspicion. In the absence of CMR, consider exercise stress testing, dobutamine stress echocardiogram, or a myocardial perfusion scan for evaluation of coronary artery disease in athletes with suspicion of prior MI or multiple risk factors for CAD.
Complete left bundle branch block	DCM HCM LVNC Sarcoidosis Myocarditis	Echocardiography CMR (with stress perfusion study)§	A comprehensive cardiac evaluation to rule out myocardial disease should be considered.
Profound nonspecific intraventricular conduction delay ≥140 ms	DCM HCM LVNC	Echocardiography	Consider additional testing based on echocardiography findings or clinical suspicion.
Epsilon wave	ARVC	Echocardiography CMR Exercise ECG test Minimum 24 h ECG monitor SAECG	An epsilon wave in leads V_1-V_3 is a highly specific ECG maker and a major diagnostic criterion for ARVC.
Multiple premature ventricular contractions	HCM DCM LVNC ARVC Myocarditis Sarcoidosis	Echocardiography 24 h ECG monitor Exercise ECG test	If >2,000 PVC's or non-sustained ventricular tachycardia are present on initial testing, comprehensive cardiac testing inclusive of CMR is warranted to investigate for myocardial disease. Consider signal averaged ECG (SAECG).
Ventricular pre-excitation	WPW	Exercise ECG test Echocardiography	Abrupt cessation of the delta wave (pre-excitation) on exercise ECG denotes a low risk pathway. EP study for risk assessment should be considered if a low risk accessory pathway cannot be confirmed by non-invasive testing. Consider EP study for moderate to high intensity sports.
Prolonged QTc	LQTS	Repeat resting ECG on separate day Review for QT prolonging medication Acquire ECG of 1st degree relatives if possible	Consider exercise ECG test, laboratory (electrolyte) screening, family screening and genetic testing when clinical suspicion is high. Consider direct referral to a heart rhythm specialist or sports cardiologist for a QTc ≥500 ms.
Brugada Type 1 pattern	Brugada syndrome	Referral to cardiologist or heart rhythm specialist	Consider high precordial lead ECG with leads V_1 and V_2 in 2nd intercostal space or sodium channel blockade if Brugada pattern is indeterminate. Consider genetic testing and family screening.
Profound sinus bradycardia <30 beats/min	Myocardial or electrical disease	Repeat ECG after mild aerobic activity	Consider additional testing based on clinical suspicion.
Profound 1° atrioventricular block ≥400 ms	Myocardial or electrical disease	Repeat ECG after mild aerobic activity Exercise ECG test	Consider additional testing based on clinical suspicion.

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ECG Abnormality	Potential Cardiac Disease*	Recommended Evaluation†	Considerations
Advanced 2° or 3° atrioventricular block	Myocardial or electrical disease	Echocardiography Minimum 24 h ECG monitor Exercise ECG test	Consider laboratory screening and CMR based on echocardiography findings.
Atrial tachyarrhythmias	Myocardial or electrical disease	Echocardiography Minimum 24 h ECG monitor Exercise ECG test	Consider CMR or EP study based on clinical suspicion.
Ventricular arrhythmias‖	Myocardial or electrical disease	Echocardiography CMR Minimum 24 h ECG monitor Exercise ECG test	A comprehensive cardiac evaluation to rule out myocardial disease and primary electrical disease should be considered.
Two or more borderline ECG findings	Myocardial disease	Echocardiography	Consider additional testing based on clinical suspicion.

*This list of disorders for each ECG abnormality represents the primary cardiac disorders of concern and is not intended to be exhaustive. †Initial evaluation of ECG abnormalities should be performed under the direction of a cardiologist. Additional testing will be guided by initial findings and clinical suspicion based on the presence of symptoms or a family history of inherited cardiac disease or SCD. ‡Excludes black athlete repolarization variant and juvenile pattern in adolescents < 16 years. §CT coronary angiography if stress perfusion with CMR is unavailable. ‖Includes couplets, triplets, accelerated ventricular rhythm, and non-sustained ventricular tachycardia.

ARVC = arrhythmogenic right ventricular cardiomyopathy; CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; DCM = dilated cardiomyopathy; ECG = electrocadiogram; EP = electrophysiological; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LVNC = left ventricular noncompaction; MI = myocardial infarction; PVC = premature ventricular contraction; SAECG = signal averaged electrocadiogram; WPW = Wolff Parkinson White syndrome.

ABNORMAL ELECTROCARDIOGRAM FINDINGS IN ATHLETES

The abnormal findings defined in this section are not recognized features of athletic training and always require further assessment to exclude the presence of intrinsic cardiac disease (**Figure 1**, **Tables 1 and 2**). Temporary restriction from athletic activity should be considered for athletes with abnormal ECGs of uncertain clinical significance until secondary investigations are completed.

ABNORMAL T-WAVE INVERSION. TWI ≥1 mm in depth in two or more contiguous leads (excluding leads aVR, III, and V_1) in an anterior, lateral, inferolateral, or inferior territory is abnormal and should prompt further evaluation for underlying structural heart disease (**Tables 1 and 2**). Normal exceptions include TWI confined to leads V_1-V_4 in black athletes when preceded by J point and/or ST-segment elevation, and TWI in leads V_1-V_3 in athletes aged < 16 years.

CLINICAL CONSIDERATIONS. The relationship between abnormal TWI and several forms of structural heart disease is well documented (56). TWI in the inferior or lateral leads is common in HCM (56–59). Whereas TWI in the right precordial leads (V_1 to V_3) or beyond in the absence of a complete RBBB is common in ARVC (**Figure 4D**) (60,61).

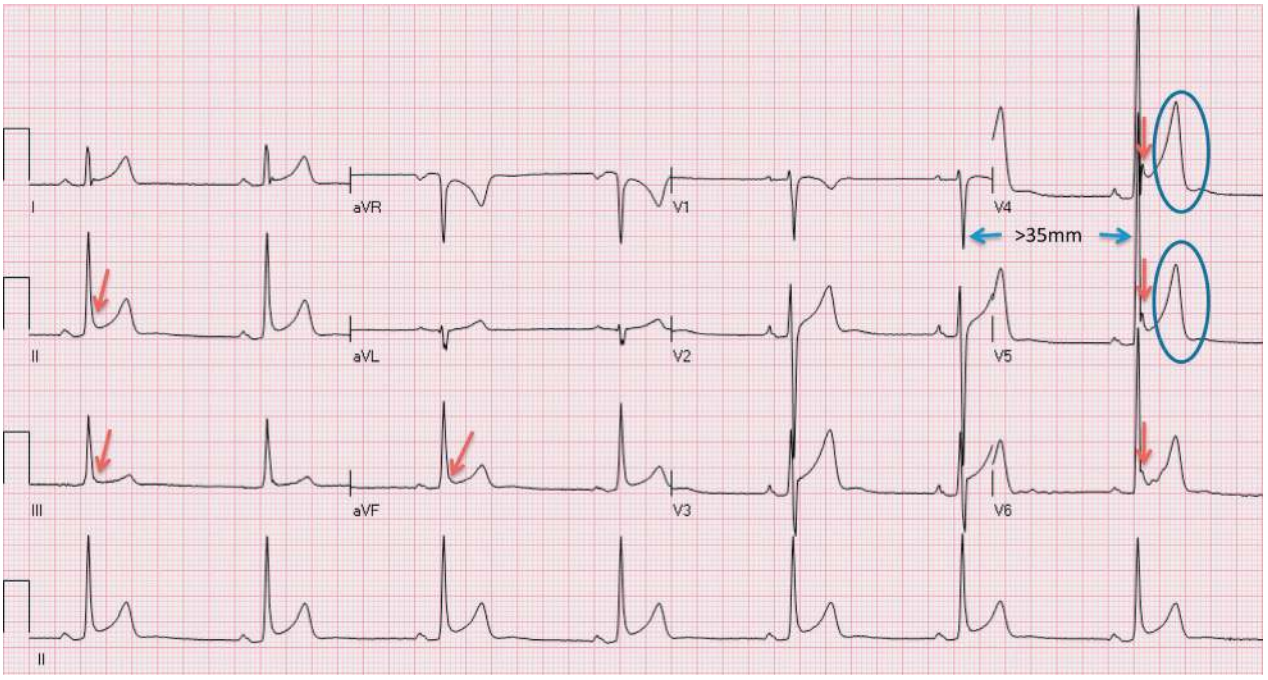
There are no data relating to the significance of flat or biphasic T-waves in athletes but similar to TWI, this panel would recommend further evaluation of biphasic T-waves where the negative portion is ≥1 mm in depth in ≥2 leads.

Evaluation. ***Lateral or inferolateral T-wave inversion.*** There is mounting evidence that TWI in the lateral or inferolateral leads is associated with the presence of quiescent cardiomyopathy in a considerable proportion of athletes (30,62–64). Recommendations for the evaluation of abnormal TWI and other clinical considerations are presented in **Table 2**.

TWI affecting the lateral leads (V_5 to V_6, I and aVL) (**Figure 4E**) should prompt a comprehensive investigation to exclude cardiomyopathy. If echocardiography is not diagnostic, cardiac magnetic resonance imaging (MRI) with gadolinium should be utilized. Cardiac MRI provides superior assessment of myocardial hypertrophy, especially the left ventricular apex and the lateral free wall and may also demonstrate late gadolinium enhancement (LGE), a non-specific marker suggesting myocardial fibrosis. If cardiac MRI is not available, echocardiography with contrast should be considered. Exercise ECG testing and Holter monitoring also should be considered in the evaluation of lateral or inferolateral TWI, especially for athletes with 'grey zone' hypertrophy (males with maximal LV wall thickness 13 to 16 mm) without LGE, where the diagnosis of HCM remains uncertain. In such cases, the presence of ventricular tachycardia during exercise or Holter may support HCM and is also useful in risk stratification (65).

For athletes with lateral or inferolateral TWI, regular follow-up with serial cardiac imaging is necessary even when the initial evaluation is normal, in order to monitor for the development of a cardiomyopathy phenotype (62,63).

Anterior T-wave inversion. Anterior TWI is a normal variant in asymptomatic adolescent athletes age <16 years, in black athletes when preceded by J-point elevation and convex ST-segment elevation, and in some endurance athletes (66,67). However, anterior



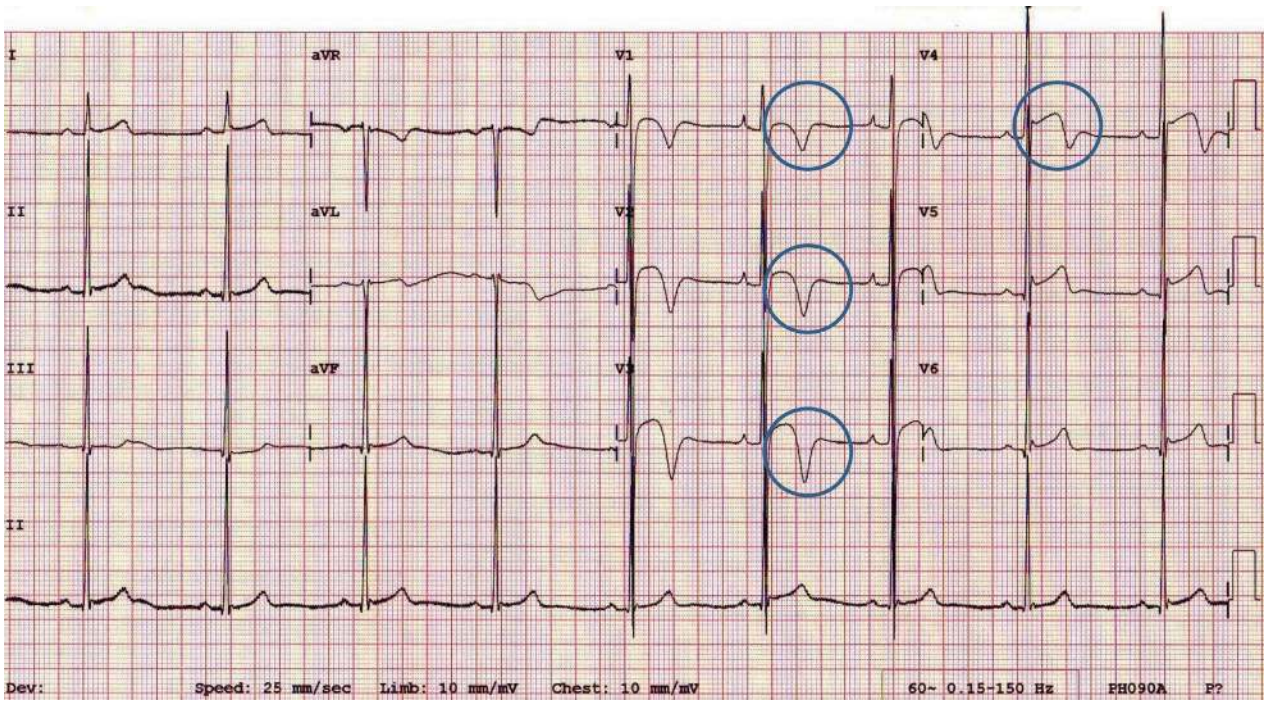
Electrocardiogram of a 29-year-old male asymptomatic soccer player showing sinus bradycardia (44 beats/min), early repolarization in I, II, aVF, V_2 to V_6 **(arrows)**, voltage criterion for left ventricular hypertrophy (S-V1 + R-V5 >35 mm), and tall, peaked T waves **(circles)**. These are common, training related findings in athletes and do not require more evaluation.

TWI in leads V_1 to V_2/V_3 also is a recognized pattern in patients with ARVC and rarely HCM.

There are discrepancies among existing guidelines relating to the extent of anterior TWI inversion before considering further investigations (5,6,14,29). A large study of over 14,000 white adults age 16 to 35 years old, including over 2,500 athletes showed that anterior TWI had a prevalence of 2.3% (68). Anterior TWI was more common in females and athletes and was confined to leads V_1 to V_2 in almost all individuals, and only exceeded beyond V_2 in 1% of females and 0.2% of males (68). None of the individuals with anterior TWI were diagnosed with a cardiomyopathy following comprehensive investigation indicating that this particular ECG pattern is non-specific in low-risk populations. Based on this report, it is justifiable to only investigate non-black athletes with anterior TWI beyond V_2 in the absence of other clinical or electrical features of ARVC.

Specific information about the J-point and preceding ST-segment may help differentiate between physiological adaptation and cardiomyopathy in athletes with anterior TWI affecting leads V_3 and/or V_4. A recent study comparing anterior TWI in a series of black and white healthy athletes, and patients with HCM and ARVC, showed that in athletes with anterior TWI, the combination of J-point elevation ≥ 1 mm and TWI confined to leads V_1 to V_4 excluded either cardiomyopathy with 100% negative predictive value, regardless of ethnicity (66). Conversely, anterior TWI associated with minimal or absent J-point elevation (<1 mm) could reflect a cardiomyopathy (66). These data require duplication in larger studies but may prove useful in the assessment of a small proportion of white endurance athletes who exhibit anterior TWI and in athletes of black/mixed ethnicity (69).

In most non-black athletes age ≥16 years, anterior TWI beyond lead V_2 should prompt further evaluation given the potential overlap with ARVC. In these athletes, concurrent findings of J-point elevation, ST-segment elevation, or biphasic T waves more likely represents athlete's heart, while the absence of J-point elevation or a coexistent depressed ST-segment is more concerning for ARVC (**Figure 5**) (66) Other ECG findings suggestive of ARVC include low limb lead voltages, prolonged S wave upstroke, ventricular ectopy with LBBB morphology, and epsilon waves (61). A combination of tests is needed to diagnose ARVC including echocardiography, cardiac MRI, Holter monitoring, exercise ECG test, and signal averaged ECG.



Electrocardiogram from a black athlete demonstrating voltage criterion for left ventricular hypertrophy, J-point elevation, and convex ('domed') ST-segment elevation followed by T-wave inversion in V_1 to V_4 **(circles)**. This is a normal repolarization pattern in black athletes.

Inferior T-wave inversion. The significance of TWI confined to the inferior leads is unknown. However, this finding cannot be attributed to physiological remodeling and thus warrants further investigation with, at minimum, an echocardiogram. Cardiac MRI should be considered based on the echocardiographic findings or clinical suspicion.

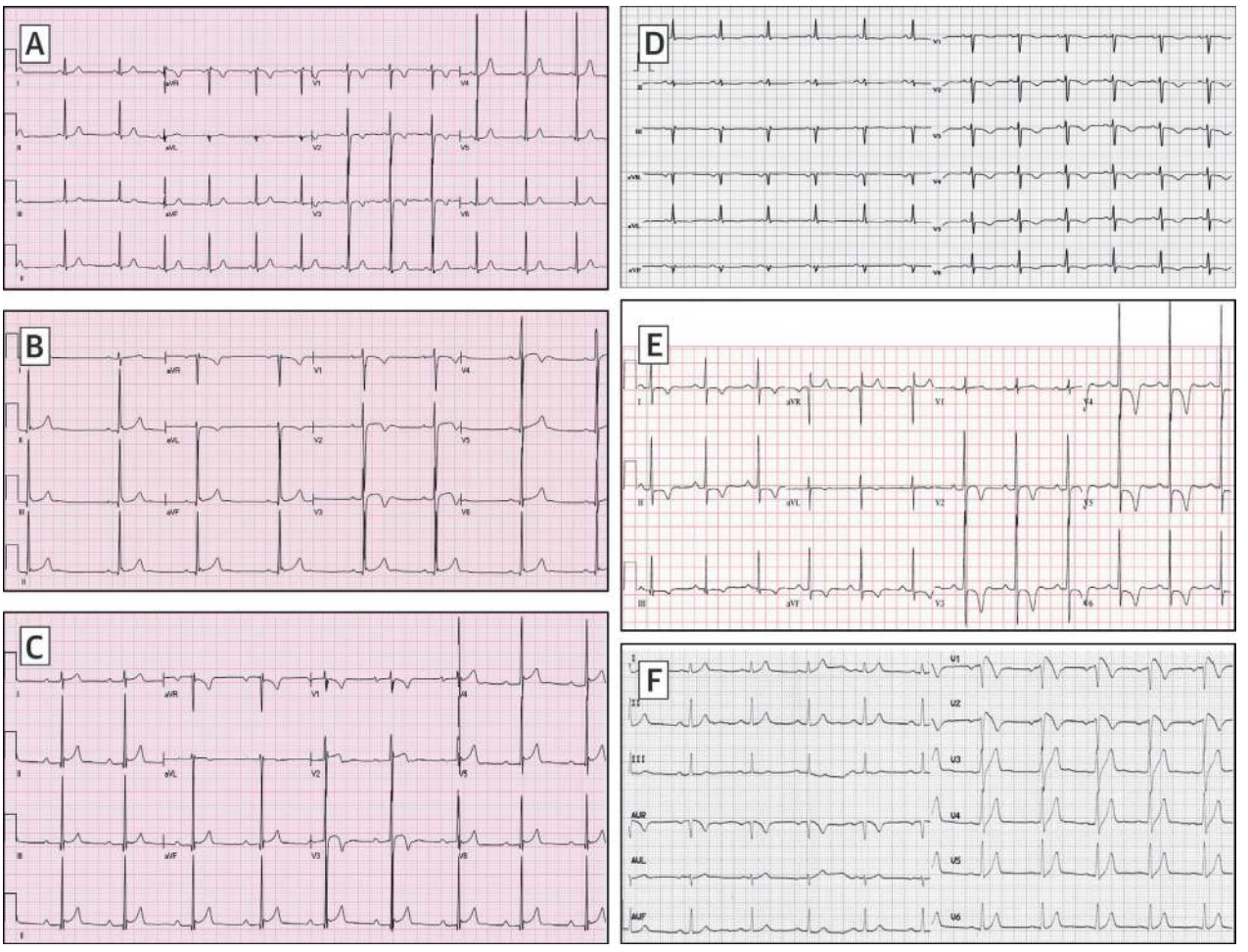
ST-SEGMENT DEPRESSION. While ST-segment depression is common among patients with cardiomyopathy, it is not a feature of athletic training (28,59,70,71). ST-segment depression (relative to the isoelectric PR segment) in excess of 0.05 mV (0.5 mm) in two or more leads should be considered an abnormal finding requiring definitive evaluation for underlying structural heart disease.

Evaluation. Echocardiography is the minimum evaluation for athletes with ST-segment depression to investigate for underlying cardiomyopathy. Cardiac MRI should be considered based on the echocardiographic findings or clinical suspicion.

PATHOLOGICAL Q WAVES. Several pathological disorders including HCM, ARVC, infiltrative myocardial diseases, accessory pathways and transmural myocardial infarction can lead to the development of exaggerated (deep or wide) Q waves or unexpected Q waves in atypical leads (28,56). Pathological Q waves also may be a result of lead misplacement. In particular, a pseudo-septal infarct pattern with pathological Q waves in leads V_1 to V_2 is commonly due to high-lead placement relative to cardiac position (72).

Pathological Q waves have been reported in approximately 1% to 2% of all athletes, and may be higher in males and black athletes (29,73). For asymptomatic athletes, pathological Q waves were previously defined as >3 mm in depth or >40 ms in duration in two or more leads (except III and aVR) (6,10). In practice, however, this criterion is a common source of false positive ECG results as trained athletes with physiological LVH and thin adolescent athletes may have increased precordial voltages and deep lateral or inferior Q waves.

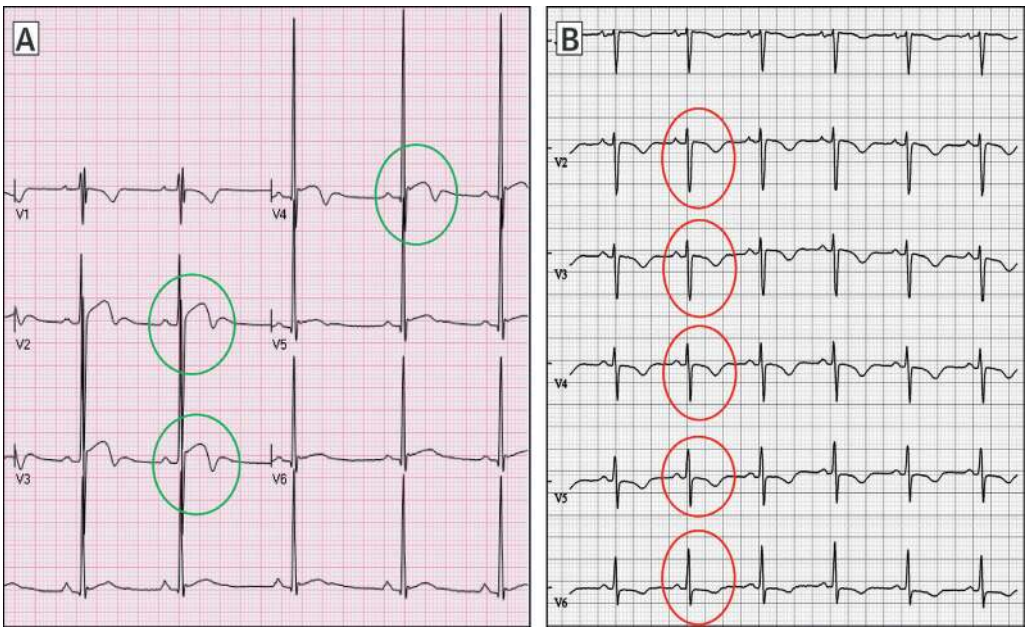
The use of a Q/R ratio overcomes some of these issues by normalizing Q wave depth to the degree of proceeding R-wave voltage. Case control analyses of athletes and HCM patients suggest that this will decrease the false positive rate without compromising sensitivity for the detection of cardiomyopathy (29,74). Thus, this consensus panel has modified the definition for pathological Q waves



(A) Anterior T-wave inversion in V_1 to V_3 in a 12-year-old asymptomatic athlete without a family history of sudden cardiac death considered a normal 'juvenile' pattern. **(B)** T-wave inversion in V_1 to V_4 in a 17-year-old asymptomatic mixed race (Middle-Eastern/black) athlete without a family history of sudden cardiac death. This is a normal repolarization pattern in black athletes. **(C)** Biphasic T-wave inversion in V_3 in a 31-year-old asymptomatic black athlete without a family history of sudden cardiac death. Anterior biphasic T waves are considered normal in adolescents <16 years old and in adults when found in a single lead, most commonly V_3. **(D)** Abnormal T-wave inversion in V_1 to V_6 in an adult symptomatic former soccer player with genetically confirmed arrhythmogenic right ventricular cardiomyopathy and a positive family history of sudden cardiac death (brother died at 26 years of age). **(E)** Inferolateral T-wave inversion in leads I, II, III, aVF, V_2 to V_6, and ST-segment depression in leads II, aVF, V_4 to V_6 in a 31-year-old asymptomatic professional soccer referee. These markedly abnormal findings require a comprehensive evaluation to exclude cardiomyopathy. **(F)** An electrocardiogram demonstrating the Type 1 Brugada pattern with high take-off ST-segment elevation ≥ 2 mm with downsloping ST-segment elevation followed by a negative symmetric T wave in V_1 to V_2.

in athletes as a Q/R ratio ≥0.25 or ≥40 ms in duration in two or more contiguous leads (except III and aVR). **Evaluation.** An ECG with abnormal Q waves should be carefully examined for the possibility of an accessory pathway. If the pathological Q waves are isolated to leads V_1 to V_2, the ECG should be repeated, including re-placing the ECG leads to ensure proper positioning. Persistence of pathological Q waves in two or more contiguous leads warrants further investigation with echocardiography to exclude cardiomyopathy. If the echocardiogram is normal and there are no other concerning clinical findings or ECG abnormalities, no additional testing is generally necessary. However, if there is a high index of clinical suspicion, additional evaluation with cardiac MRI should be considered. In athlete's age ≥30 years with suspicion of prior myocardial infarction or risk factors for coronary artery disease (CAD), stress testing may be warranted.

COMPLETE LEFT BUNDLE BRANCH BLOCK. LBBB is found in <1 in 1,000 athletes but is common in patients with cardiomyopathy and ischemic heart



(A) T-wave inversion in V_1 to V_4 preceded by J-point elevation and convex 'domed' ST-segment elevation **(green circles)**. This should not be confused with pathological T-wave inversion **(B)** which demonstrates T-wave inversion in V_1 to V_6 with absent J-point elevation and a downsloping ST-segment **(red circles)**.

disease (9,28,59,75,76). Thus, complete LBBB always should be considered an abnormal finding and requires a comprehensive evaluation to rule out a pathological cardiac disorder.

Evaluation. Athletes with complete LBBB require a thorough investigation for myocardial disease including echocardiography and a cardiac MRI with perfusion study.

PROFOUND NON-SPECIFIC INTRA-VENTRICULAR CONDUCTION DELAY. Epidemiological studies of nonspecific intra-ventricular conduction delay (IVCD) in the general population have shown an increased risk of cardiovascular death and have been documented among patients with cardiomyopathy (77,78). The significance of non-specific IVCD with normal QRS morphology in healthy, asymptomatic athletes is uncertain (79). The physiology underlying IVCD in athletes remains incompletely understood but likely includes some combination of neurally mediated conduction fiber slowing and increased myocardial mass. In patients with LVH, left ventricular mass seems to be closely related to QRS duration (80).

While the exact cut-off to trigger more investigation in athletes with a nonspecific IVCD remains unclear, this panel recommends that marked nonspecific IVCD ≥140 ms in athletes, regardless of QRS morphology, is abnormal and should prompt further evaluation.

Evaluation. In asymptomatic athletes with profound non-specific IVCD, an echocardiogram is recommended to evaluate for myocardial disease. Other testing may be indicated depending on echocardiographic findings or clinical suspicion.

VENTRICULAR PRE-EXCITATION. Ventricular pre-excitation occurs when an accessory pathway bypasses the AV node resulting in abnormal conduction to the ventricle (pre-excitation) with shortening of the PR interval and widening of the QRS. This is evident on the ECG as the Wolf-Parkinson-White (WPW) pattern defined as a PR interval <120 ms, the presence of a delta wave (slurring of the initial QRS), and a QRS duration >120 ms (81). The WPW pattern occurs in up to 1 in 250 athletes (9,12,52,82). The presence of an accessory pathway can predispose an athlete to sudden death because rapid conduction of atrial fibrillation across the accessory pathway can result in VF.

Evaluation. A short PR interval in isolation without a widened QRS or delta wave in an asymptomatic athlete should not be considered for further assessment. The WPW pattern warrants further assessment of the

refractory period of the accessory pathway. Non-invasive risk stratification begins with an exercise stress test, where abrupt, complete loss of pre-excitation at higher heart rates suggests a low-risk accessory pathway (83,84). An echocardiogram also should be considered due to the association of WPW with Ebstein's anomaly and cardiomyopathy. Intermittent pre-excitation during sinus rhythm on a resting ECG is also consistent with a low-risk pathway and may obviate the need for an exercise test (85). If non-invasive testing cannot confirm a low-risk pathway or is inconclusive, an electrophysiological study should be considered to determine the shortest pre-excited RR interval during atrial fibrillation (83). If the shortest pre-excited RR interval is ≤250 ms (240 beats/min), then the accessory pathway is deemed high risk and transcatheter ablation is recommended (83,86). Some physicians may choose to subject all competitive athletes involved in moderate or high-intensity sport to electrophysiological studies irrespective of the results of the exercise test or 24 h ECG on the premise that high catecholamine concentrations during very intensive exercise may modify the refractory period of an accessory pathway in a fashion that cannot be reproduced during laboratory tests.

PROLONGED QT INTERVAL. Congenital long QT syndrome (LQTS) is a potentially lethal, genetically mediated ventricular arrhythmia syndrome with the hallmark electrocardiographic feature of QT prolongation. LQTS is estimated to affect 1 in 2,000 individuals, and this may be underestimated given the subpopulation of so-called 'normal QT interval' or 'concealed' LQTS (87). Autopsy negative sudden unexplained death represents 25% to 40% of sudden unexpected deaths in persons under age 40 years (3,88-90). In such cases, cardiac ion channelopathies have been implicated by post-mortem genetic testing as the probable cause in up to 25% to 40% of cases (91-94).

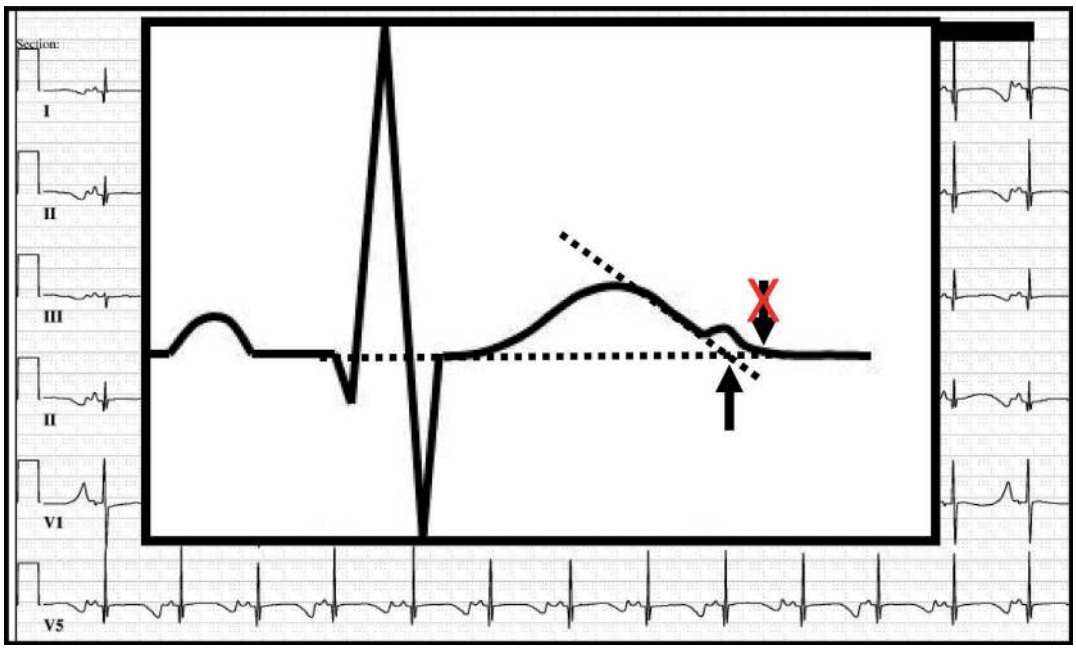
Calculating the corrected QT interval. Accurate measurement and manual confirmation of the computer derived QT interval corrected for heart rate (QTc) is critical as the accuracy of computer generated QTc values is about 90% to 95%. Studies have suggested the ability of cardiologists to accurately measure the QTc is suboptimal (95). However, accurate assessment of the QTc can be achieved by adhering to the following six principles (96):

1. Use Bazett's heart rate correction formula (QTc = QT/√RR; note the RR interval is measured in seconds) as population-based QTc distributions most frequently use Bazett-derived QTc values (97).
2. Bazett's formula underestimates the QTc at heart rates <50 beats/min, and overestimates the QTc at heart rates >90 beats/min. Accordingly, for a heart rate <50 beats/min, a repeat ECG after mild aerobic activity is recommended to achieve a heart rate closer to 60 beats/min. For heart rates >90 beats/min, a repeat ECG after additional resting time may help achieve a lower heart rate.
3. If sinus arrhythmia is present with beat to beat variation in heart rate, an average QT interval and average RR interval should be used.
4. Leads II and V_5 usually provide the best delineation of the T-wave.
5. Low amplitude U waves, which are common in the anterior precordial leads, should not be included in the QT calculation. The 'Teach-the-Tangent' or 'Avoid-the-Tail' method to delineate the end of the T-wave should be followed (**Figure 6**) (96).
6. The morphology of the T-wave, not just the length of the QT interval, also can suggest the presence of LQTS (98). For instance, a notched T-wave in the lateral precordial leads where the amplitude of the second portion of the T-wave following the notch is greater than the first portion of the T-wave may represent LQT-2 even in the absence of overt QT prolongation.

The easiest and most efficient way to confirm the computer-derived QTc is to examine lead II and/or V_5 and determine if the manually measured QT interval matches the computer's QT measurement. If there is concordance within about 10 ms, one can trust that the computer can derive accurately an average RR interval and complete the Bazett's calculation. If, however, the manually measured QT interval is >10 ms different than the computer's QT measurement, an average RR interval should be determined and the QTc recalculated using the Bazett's formula.

Corrected QT cut-offs. Given the overlap between QTc distributions in population-derived cohorts of healthy individuals compared with patients with genetically confirmed LQTS, the QTc cut-off value compelling further evaluation must be chosen carefully to balance the frequency of abnormal results and the positive predictive value for LQTS.

Recent consensus statements on ECG interpretation in athletes have recommended that male athletes with a QTc ≥470 ms and female athletes with a QTc ≥480 ms undergo further evaluation for LQTS to better balance false positive and false negative findings (6,10). These cut-off values are around the 99th percentile and consistent with thresholds defined by the American Heart Association and



A straight line is drawn on the downslope of the T-wave to the point of intersection with the isoelectric line. The U-wave is not included in the measurement.

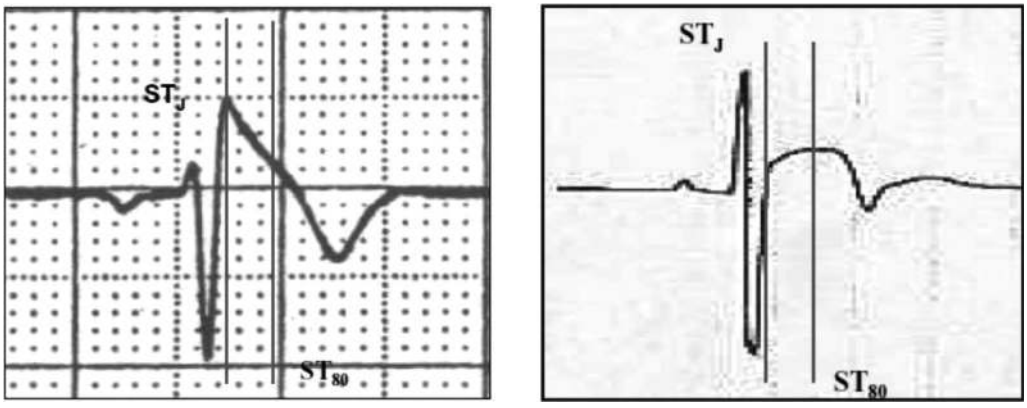
American College of Cardiology (99). This consensus group also recommends QTc values of ≥470 ms in males and ≥480 ms in females to define the threshold of QT prolongation that warrants further assessment in asymptomatic athletes.

Short QT interval. The precise cut-off and clinical significance of a short QT interval in athletes is unknown. Data from over 18,000 asymptomatic young British individuals found that the prevalence of a QTc <320 ms is 0.1%; suggesting an abnormal cut-off value of <320 ms is pragmatic (100). However, over a mean follow up period of 5.3 years, none of the individuals with a short QT <320 ms experienced any adverse events, syncope, or sudden death (100). Based on the rarity of this finding and absence of data to suggest long-term morbidity in asymptomatic athletes, this panel recommends that a short QT interval only be investigated in the context of concerning clinical markers.

Evaluation. It is critical that an athlete with a single prolonged QTc reading not be obligated a diagnosis of LQTS, but rather that these cut-off values trigger the need for additional evaluation. The importance of additional evaluation but not a premature diagnosis of LQTS was demonstrated in a study of 2,000 elite athletes in which 7 (0.4%) had a prolonged QTc (range 460 to 570 ms) (101). A QTc of <500 ms in the absence of symptoms or familial disease was unlikely to represent LQTS. In contrast, a QTc ≥500 ms was highly suggestive of LQTS as all three athletes with a QTc value of >500 ms exhibited one of paradoxical prolongation of the QTc during exercise, a confirmatory genetic mutation, or prolonged QTc in a first-degree relative (101).

A personal history of syncope or seizures and a family history of exertional syncope, ‘epilepsy’, postpartum-timed syncope/seizure, unexplained motor vehicle accidents, unexplained drowning, and premature, unexplained sudden death <50 years of age should be reviewed. If the personal/family history is positive, the athlete should be referred to an electrophysiologist for further evaluation. If the personal/family history is negative, a repeat ECG should be obtained (ideally on a different day). If the follow-up ECG is below the QTc cut-off values, then no additional evaluation is needed and the athlete should be reassured.

If the repeat ECG still exceeds the QTc cut-off values, then a screening ECG of the athlete’s first degree relatives (parents and siblings) should be considered and the athlete should be referred to an electrophysiologist for the possibility of newly



Brugada Type 1 electrocardiogram **(left)** should be distinguished from early repolarization with 'convex' ST-segment elevation in a trained athlete **(right)**. **Vertical lines** mark the J-point (STJ) and the point 80 ms after the J-point (ST80), where the amplitudes of the ST-segment elevation are calculated. The 'downsloping' ST-segment elevation in Brugada pattern is characterized by a STJ/ST80 ratio >1. Early repolarization patterns in an athlete show an initial 'upsloping' ST-segment elevation with STJ/ST80 ratio <1.

discovered LQTS. Reversible, extrinsic factors, such as electrolyte abnormalities (hypokalaemia) or the presence of QT prolonging medications, must also be evaluated. If an athlete's ECG shows a QTc ≥500 ms and no reversible causes are identified, then the athlete should be referred immediately to an electrophysiologist as the probability of LQTS and future adverse events has increased (102). The Schwartz-Moss scoring system, electrocardiographic features, stress ECG, provocative testing, and genetic testing may be needed to clarify the diagnosis and should be performed and interpreted by a cardiologist familiar with the disease (103-106).

BRUGADA TYPE 1 PATTERN. Brugada syndrome (BrS) is an inherited primary electrical disease which predisposes to ventricular tachyarrhythmias and sudden death during states of enhanced vagal tone. It is characterized by the distinctive Brugada ECG pattern which consists of a coved rSr' pattern, ST-segment elevation ≥2 mm, and inversion of the terminal portion of the T-wave in leads V_1, V_2, and V_3 (**Figure 4F**). Although three types were described, only the Type 1 Brugada pattern is now considered diagnostic (107-109).

The coved ST-segment elevation in Type 1 Brugada pattern results in a broad r' and should be distinguishable from the upsloping ST-segment elevation of early repolarization in an athlete. In this regards, the 'Corrado index' measures the ST-segment elevation at the start of the ST-segment/J-point (STJ) and 80 ms after the start of the ST-segment (ST80) (110). In Type 1 Brugada pattern, the downsloping ST-segment will have a STJ/ST80 ratio >1, while the initial upsloping of the ST-segment found in early repolarization patterns in an athlete will produce an STJ/ST80 ratio <1 (**Figure 7**).

Evaluation. The Type 1 Brugada ECG pattern should be investigated regardless of symptoms. If the pattern is unclear, confirm correct lead placement, repeat the ECG if necessary, and perform a high precordial lead ECG with V_1 and V_2 placed in the 2nd or 3rd intercostal space. If the Type 1 pattern is seen on a high-precordial lead ECG, then referral to an electrophysiologist is indicated. Consideration should be given to potential accentuating factors for a Brugada-like ECG pattern, such as hyperkalaemia, fever, medications with sodium ion channel blocking properties, and lead placement.

PROFOUND SINUS BRADYCARDIA OR FIRST DEGREE ATRIOVENTRICULAR BLOCK. Sinus bradycardia and moderate prolongation of the PR interval (200-399 ms) are recognized features of athletic conditioning. Although a resting heart rate ≤30 beats/min or a PR interval ≥400 ms may be normal in a well-trained athlete, it should prompt further evaluation for cardiac conduction disease.

Evaluation. Evaluation of profound sinus bradycardia or a markedly increased PR interval should include assessing the chronotropic response to mild aerobic activity, such as running on the spot or climbing stairs. Exercise testing is useful in this

situation to provide an objective measure of the PR interval and heart rate response to aerobic activity. If the heart rate increases appropriately and the PR interval normalizes, and the athlete is asymptomatic, no further testing is necessary. Conversely, further evaluation should be performed if the heart rate does not increase or the PR interval does not shorten appropriately on exertion, the athlete experiences pre-syncope/syncope, or in athletes with a family history of cardiac disease or sudden death. Depending on the clinical scenario, an echocardiogram or ambulatory ECG monitor may be indicated.

HIGH GRADE ATRIOVENTRICULAR BLOCK. Mobitz Type II second degree AV block and third degree (complete) AV block are abnormal findings in athletes. Complete heart block can be confused with AV dissociation without block; a situation where the junctional pacemaker is faster than the sinus node, leading to more QRS complexes than P waves. Intermittent ventricular capture by sinus P waves (resulting in an irregular ventricular response) excludes complete AV block. AV dissociation without block is the expression of autonomic mismatch between AV and sinus nodal modulation, but is not pathological. Like all other functional disturbances, a small exercise load with repeat ECG recording will show resolution of the ECG findings in AV dissociation.

Evaluation. If Mobitz II AV block or complete AV block is detected, further evaluation includes an echocardiogram, ambulatory ECG monitor, and exercise ECG test. Based on these results, laboratory testing and cardiac MRI may be considered. Referral to an electrophysiologist is essential.

MULTIPLE PREMATURE VENTRICULAR CONTRACTIONS. Multiple (≥2) premature ventricular contractions (PVCs) are uncommon and present in <1% of 12-lead ECGs in athletes (9,12). Although multiple PVCs are usually benign, their presence may be the hallmark of underlying heart disease (111,112). PVCs originating from the right ventricular outflow tract (LBBB and inferior axis origin) are considered particularly benign when associated with a normal ECG, however this PVC morphology can also be present in patients with early ARVC particularly when the QRS exceeds 160 ms (113). Therefore, the finding of ≥2 PVCs on an ECG should prompt more extensive evaluation to exclude underlying structural heart disease.

Evaluation. The extent of evaluation for ≥2 PVCs is controversial and excluding pathology may be difficult. At a minimum, an ambulatory Holter monitor, echocardiogram, and exercise stress test should be performed. The availability of modern small, leadless ambulatory recorders allows for longer electrocardiographic monitoring, including during training and competition, to exclude complex ventricular arrhythmias. If the Holter and echocardiogram are normal and the PVCs suppress with exercise, no further evaluation is recommended for an asymptomatic athlete. A previous study has shown that among athletes with ≥2,000 PVCs per 24 h, up to 30% were found to have underlying structural heart disease, compared with 3% and 0% in those with <2,000 and <100 PVCs per day, respectively (112). Therefore, in athletes with ≥2,000 PVCs per 24 h or with episodes of non-sustained ventricular tachycardia, or with an increasing burden of ectopy during an incremental exercise test, additional evaluation may include contrast-enhanced cardiac MRI and more invasive electrophysiology study (114,115). Although some studies have suggested that regression of the PVC burden with detraining indicates a good prognosis, other studies have not confirmed this (116–118). Thus, detraining as a diagnostic or therapeutic measure is not recommended.

ATRIAL TACHYARRHYTHMIAS. Sinus tachycardia is the most common atrial tachyarrhythmia but is very rarely due to intrinsic cardiac disease. Supraventricular tachycardia (SVT), atrial fibrillation, and atrial flutter are rarely seen on a resting ECG in athletes and require investigation. Atrial tachyarrhythmias are rarely life threatening but can be associated with other conditions that can lead to SCD, including LQTS, WPW, BrS, myocarditis, congenital heart disease, and the cardiomyopathies.

Evaluation. If resting sinus tachycardia >120 beats/min is seen, a repeat ECG should be considered after a period of rest as recent exercise or anxiety may be the cause. Other underlying etiologies may be sought, including fever, infection, dehydration, stimulant use, anemia, hyperthyroidism, or, rarely, underlying cardiac or pulmonary disease.

For paroxysmal SVT, a repeat ECG when not in SVT should be obtained if possible. If the Valsalva maneuver, carotid sinus massage, or the diving reflex is used to terminate the arrhythmia, a rhythm strip should be obtained which can help elucidate the mechanism of the SVT. An echocardiogram, ambulatory ECG monitor, and exercise treadmill test should be completed. Referral to an electrophysiologist may be indicated for consideration of electrophysiology study and ablation.

If atrial fibrillation or flutter is found, an echocardiogram should be completed to assess for structural heart disease and anti-coagulation considered based on standard guidelines (119). An ambulatory ECG

monitor should be used to assess if the rhythm is paroxysmal or persistent and what the ventricular rate is throughout the day. A thorough family history may elucidate an underlying genetic cause. Depending on what these results show, cardiac MRI, electrophysiology study with possible ablation, and/or genetic testing may be considered.

VENTRICULAR ARRHYTHMIAS. Ventricular couplets, triplets, and non-sustained ventricular tachycardia always require investigation as they can be a marker for underlying cardiac pathology or lead to sustained ventricular tachycardia which may cause SCD.

Evaluation. If ventricular arrhythmias are seen, the evaluation should include a thorough family history, an echocardiogram to evaluate for structural heart disease, cardiac MRI to assess for ARVC or other cardiomyopathies, ambulatory ECG monitor and exercise ECG test. Depending on these results, further evaluation may be needed including electrophysiology study or genetic testing.

CONSIDERATIONS IN ATHLETES ≥30 YEARS OF AGE. In athletes ≥30 years of age, CAD is the most common cause of SCD (89,90). In addition, older athletes may be less fit compared with 20 to 30 years ago, increasing the possibility of underlying CAD (120,121). While resting ECGs have a low sensitivity for CAD, some ECG patterns may suggest underlying CAD such as TWI, pathological Q waves, ST-segment depression, left or RBBB, abnormal R-wave progression, left anterior hemiblock, and atrial fibrillation (122–124).

Evaluation. The main role of a resting ECG in older athletes is to identify those athletes who may potentially be at high risk for CAD and warrant further testing (123,125,126). Initial testing should include an exercise stress test, resting echocardiogram, and assessment of traditional risk factors for CAD. When indicated, this evaluation may be complemented by coronary CT angiography or a functional stress test.

ELECTROCARDIOGRAM PATTERNS REQUIRING SERIAL EVALUATION. Several common heritable cardiomyopathies may present with ECG abnormalities prior to the onset of overt heart muscle pathology (62,63). Therefore, athletes with abnormal ECGs suggestive of cardiomyopathy and initially normal clinical evaluations should be followed with serial evaluation during and after their competitive athletic careers. Evaluations may be conducted annually or more frequently depending on individual circumstances. These athletes may be permitted to participate in competitive athletics without restriction contingent on longitudinal follow-up.

CONCLUSION

Accurate ECG interpretation in athletes requires adequate training and an attention to detail to distinguish physiological ECG findings from abnormal ECG findings that might indicate the presence of cardiac pathology. The international consensus standards presented on ECG interpretation and the evaluation of ECG abnormalities serve as an important foundation for improving the quality of cardiovascular care of athletes. As new scientific data become available, revision of these recommendations may be necessary to further advance the accuracy of ECG interpretation in the athletic population.

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KEY WORDS athlete, electrocardiogram

APPENDIX For supplemental material containing an extended account of the document and additional illustrative ECGs, please see the online version of this article.

STATE-OF-THE-ART REVIEW ARTICLE

Echocardiography: Profiling of the Athlete's Heart

Timothy E. Paterick, MD, JD, Tia Gordon, RDCS, and Denise Spiegel, RDCS, *Milwaukee, Wisconsin*

Cardiovascular physiologic remodeling associated with athleticism may mimic many of the features of genetic and acquired heart disease. The most pervasive dilemma is distinguishing between normal and abnormal physiologic remodeling in an athlete's heart. Imaging examinations, such as magnetic resonance imaging and computed tomography, which focus predominantly on anatomy, and electrocardiography, which monitors electrical components, do not simultaneously evaluate cardiac anatomy and physiology. Despite nonlinear anatomic and electrical remodeling, the athlete's heart retains normal or supernormal myocyte function, whereas a diseased heart has various degrees of pathophysiology. Echocardiography is the only cost-effective, validated imaging modality that is widely available and capable of simultaneously quantifying variable anatomic and physiologic features. Doppler echocardiography substantially redefines the understanding of normal remodeling from preemergent and overt disease. (J Am Soc Echocardiogr 2014;27:940-8.)

Keywords: Athletic training, Adaptive cardiac remodeling, Athletic heart, Structural heart disease, Echocardiography

The athletic heart's structural and functional changes intrigue those in the medical community who care for the athlete population.[1] Intense or chronic athletic training prompts complex remodeling of the anatomy and physiology of the heart to accommodate a state of enhanced cardiovascular performance.[1] The distinction between adaptive and maladaptive remodeling is the fundamental challenge in accurately defining individualized risk in athletes.[2] Typically, an athletic heart is associated with cardiac chamber enlargement, increased left ventricular (LV) mass and modest aortic root enlargement to accommodate increased physiologic demands. Adapted morphology and physiology vary considerably among athletes and are affected by each individual's form and intensity of athletic training.[3] Cardiovascular remodeling is nonlinear, meaning that any particular feature can change unpredictably and vacillate between normal and abnormal during the remodeling process. Myocardial adaptation and performance are unique to each individual athlete and represent complex nonlinear interactions between multiple organ and physiologic systems.[4]

Although conventional pathophysiologic guided diagnostics and therapeutics have been used for decades, there are significant limitations that are particularly challenging.[5] Disease is rarely a consequence of a single effector but rather a reflection of a set of morphophysiologic processes that interact in a complex network. (i.e., a module composed of closely related features is discernible only by appreciating the behavior of the network as a whole rather than its individual components). This shortcoming accounts for many limitations of defined disease determinants and design of rational decisions. This background highlights the need to reconsider and redefine the determinants of cardiovascular risk in athletes and the logic of implementing clinical Doppler echocardiographic classification methods.

In this report, we review the physiologic and morphologic features associated with variable athletic training in endurance and strength athletes, the incidence and associations of sudden cardiac death (SCD) in athletes, and the importance of personal and family history and physical examination in guiding diagnostic testing. We offer a detailed discussion of how echocardiography plays an essential role in distinguishing adaptive from maladaptive remodeling.

The distinction between adaptive and maladaptive remodeling requires an understanding of the evolving myocyte changes temporally. In disease states, there is an early transition from normal to abnormal myocyte function, followed by longitudinal myocyte dysfunction (manifested as a reduction in early diastolic mitral annular tissue velocity [e′]), followed by diastolic strain, strain rate, and twist dysfunction and, ultimately, global systolic strain rate (indicating fibrosis and cell death). The athletic heart begins with hypernormal function. The athlete's heart continues to be normal or hypernormal, whereas the diseased heart evolves along a cascade from early abnormal myocyte dysfunction to myocardial dysfunction. This distinction is illustrated when comparing athletic heart and hypertrophic cardiomyopathy (HCM) (Table 1).

REMODELING FEATURES

Athletic heart exhibits complex, variable physiologic states. For example, intense physical exercise enhances cardiac output six- to eightfold and increases pulmonary oxygen uptake. An athlete's heart rate can range from <40 beats/min at rest to >220 beats/min at peak exertion. The dynamic changes in LV relaxation in the athletic heart account for the increased stroke volume and cardiac output at extreme heart rates. The body's cardiovascular network is a fine-tuned, nonlinear feedback system. The contiguous architecture of the cardiovascular system (atria, ventricles, and aorta) undergoes continuous nonlinear remodeling that reflects adaptive changes in both athletic and disease states (i.e., a state of ongoing change or "flux"). A disease with a contiguous system is referred to as a "continuity disease." An example of a continuity disease is hypertension, which causes abnormal aortic pressure with negative feedback to

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Abbreviations

ARVD = Arrhythmogenic right ventricular dysplasia

HCM = Hypertrophic cardiomyopathy

LV = Left ventricular

MRI = Magnetic resonance imaging

RV = Right ventricular

SCD = Sudden cardiac death

the ventricles and, subsequently, the atria, resulting in remodeling of the adjacent cardiac chambers of the contiguous cardiovascular system.

ENDURANCE VERSUS STRENGTH TRAINING

Individual athletic disciplines result in individualized variability of cardiovascular remodeling, which reflects the nature and intensity of the individual athletic activity. Endurance exercise involves sustained elevation in cardiac output with reduced peripheral vascular resistance, resulting in a continuous volume challenge for all cardiac chambers. Long-distance running, cycling, and swimming represent endurance exercise. Alternatively, strength training involves exercise activities that are characterized by cardiac output that is normal or slightly elevated and increased peripheral vascular resistance; this results in increased blood pressure and LV afterload. Weightlifting, football, and wrestling are athletic disciplines representative of strength training. Overlap sports, including soccer, basketball, and hockey, encompass significant constituents of endurance and strength exercise training. The variable hemodynamic effects play a major role in the degree and type of individualized cardiovascular remodeling.

INDIVIDUAL MORPHOLOGY AND PHYSIOLOGY

Before an echocardiographic evaluation, there must be a comprehensive medical evaluation. The athlete's health profile, including supine and standing blood pressure, heart rate, venous and arterial examination, and cardiac auscultation, should be recorded. The athlete's medical history, personal family history, and type and intensity of athletic activity must be obtained and recorded. This background information will guide the type of testing needed. Perfunctory stress and electrocardiographic testing is usually of little value and is associated with false-positive results, which can markedly increase ancillary costs.[6] Screening stress tests are not cost effective.[7-9]

INCIDENCE AND ASSOCIATIONS OF SUDDEN CARDIAC DEATH

Approximately 50% of all athletic deaths are due to unanticipated accidents.[10] Most common forms of disease associated with SCD are attributed to structural and physiologic cardiovascular disease that predispose athletes to fatal events. HCM is the disease most commonly associated with cardiac sudden death in the United States. Arrhythmogenic right ventricular (RV) dysplasia (ARVD) is the disease most commonly associated with cardiac sudden death in Italy. Arrhythmogenic syndromes, such as ion channelopathies, are relatively uncommon causes of SCD that typically lack evidence of structural heart disease. Sports-related SCD in the general population is considerably more common than previously suspected.[11] The cardiovascular sudden death rate in college athletes is higher than previous reports in high school athletes.[12] The determinants of these finding are uncertain, but they are potentially attributable to the longer exposure of college athletes to rigorous training regimens and longer durations of training. Drug and alcohol accessibility may be responsible for the higher sudden death rate in college athletes.[12] Black college athletes are at a fivefold greater risk for cardiovascular sudden death than white athletes.[13] Male athletes' risk for SCD exceeds that for female athletes by three- to sixfold.[14]

Table 1 Distinguishing athlete's heart from HCM

Data feature	Athlete's heart	HCM	Value
Increased wall thickness	Yes	Yes	No
Atrial remodeling	Yes	Yes	No
Systolic function	Normal	Normal	No
Mechanical function (strain)	Normal	Abnormal	Yes
Diastolic physiology	Normal	Abnormal	Yes

Data from Paterick TE, Jan MF, Paterick ZR, Umland MM, Kramer C, Lake P, et al. Cardiac evaluation of collegiate student athletes: a medical and legal perspective. Am J Med 2012;125:742–752.

MORPHOPHYSIOLOGIC ECHOCARDIOGRAPHY

Echocardiography is the most logical means of defining and quantifying normal and abnormal physiology and morphology in a single examination. Combining cardiac morphology and physiology is recommended as the most definitive way to classify cardiovascular risk in most athletes.[15] Imaging modalities that do not incorporate simultaneous physiologic information provide much less useful discriminatory information.

SPECIFIC FEATURES OF ATHLETIC HEART

The Left Ventricle

The athletic heart typically has increased chamber dimensions and increased LV wall thickness. These findings often mimic the echocardiographic features of diseases affecting the left ventricle.[16-18] These unique findings of increased wall thickness and LV dilation are more common in athletes who engage in the most strenuous levels of exercise training.[19]

The unique remodeling of endurance athletes results in eccentric hypertrophy, in which there is increased wall thickness and chamber dilation. Strength-trained athletes display thickening of the LV wall with mild LV dilation, resulting in concentric hypertrophy. Combination athletes typically display a phenotype with overlapping features of endurance and strength-trained athletes.[18] LV eccentric and concentric hypertrophy, without physiologic classification, can be inappropriately misinterpreted as HCM.

Increased LV wall thickness results from chamber pressure, volume overload, or both.[20,21] The true phenotypic expression is often a combination of pressure and volume overload of the myocardium. Concentric remodeling increases the relative wall thickness without an increase in LV mass.[22] The remodeling of the left ventricle is more eccentric in endurance athletes, but athletes often maintain balanced hypertrophy.[23] In general, athletes more commonly have concentric remodeling. Extreme LV remodeling occurring in some ultra-elite athletes has raised a concern as to whether such extreme morphologic adaptation has potential adverse clinical consequences, as 10% to 45% of elite endurance athletes have LV cavity end-diastolic dimensions $>$ 60 mm. This magnitude of enlargement is identified in pathologic forms of dilated cardiomyopathy.[17] The

Table 2 LV characteristics in athletes and nonathletes

LV function	Athletes	Nonathletes
Morphology		
IVSd (mm)	8–13	6–10
LVIDd (mm)	49–65	42–59
LVM (g)	113–400	88–224
Volumes/EF		
LV EDV (mL)	130–240	67–155
LV EF (%)	45–70	>55
Tissue Doppler		
Sm (cm/sec)	6.5–14	>6
e′ (cm/sec)	7.5–16	>8
Mechanical parameter		
Strain/strain rate	Similar to nonathletes (GLS > −18%)	GLS > -18%

EDV, End-diastolic volume; *EF*, ejection fraction; *GLS*, global longitudinal strain; *IVSd*, interventricular septal thickness at diastole; LVIDd, LV internal diameter at diastole; LVM, LV mass; *Sm*, tissue Doppler imaging peak velocity at systole.
Data from Paterick TE, Jan MF, Paterick ZR, Umland MM, Kramer C, Lake P, et al. Cardiac evaluation of collegiate student athletes: a medical and legal perspective. Am J Med 2012;125:742–752.

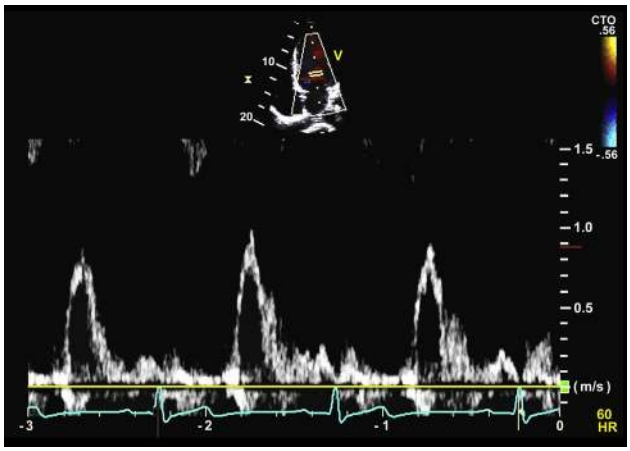

Figure 1 Pulsed-wave Doppler of mitral inflow obtained by placing the pulsed-wave Doppler gate at the very tip of the mitral valve leaflets in the apical four-chamber window: Doppler tracing reveals superior early diastolic filling as assessed by E-wave velocity and near absence of the A wave. This is characteristic of an endurance-trained athlete.

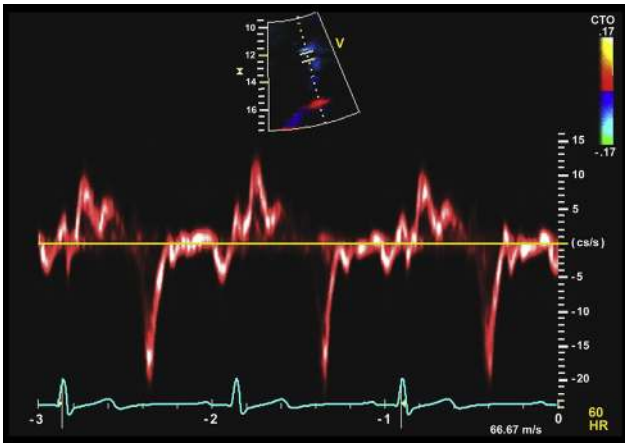

Figure 2 In the apical four-chamber view, a 2-mm pulsed-wave Doppler gate is placed at the medical annulus, obtaining the peak early diastolic, atrial, and systolic tissue velocities. Tissue Doppler reveals supernormal peak early diastolic velocity (e′) and annular systolic tissue velocities (Sm) This represents super competent diastolic function characteristic of adaptive remodeling from intense athletic training.

severe remodeling may not reverse in all elite athletes with deconditioning; chamber enlargement persists in 20% of retired elite athletes after 5 years.[24] There is no available evidence that cardiac remodeling from intense physical training results in LV disease or SCD. These measurements of LV mass and muscle distribution have little role in definitively distinguishing physiologic from maladaptive remodeling in athletes. Healthy athletes and healthy nonathletes can be distinguished morphologically and physiologically (Table 2).

LV Diastolic Function. LV diastolic function must be integrated with LV systolic function to comprehensively appraise the athletic heart. Diastolic dysfunction typically precedes systolic dysfunction. Most important, athletic hearts do not accrue diastolic or systolic dysfunction. Trained athletes have enhanced early diastolic LV filling, depicted by increased E-wave velocity and near absence of the A wave, in addition to supernormal medial annular tissue Doppler velocities[25,26] (Figures 1 and 2, Video 1; available at www.onlinejase.com). The proficient diastolic function of endurance-trained athletes allows the left ventricle to relax briskly during extremes in heart rate, allowing the preservation of stroke volume. Cardiac diastolic function is a critical factor in distinguishing adaptive remodeling from disease remodeling.[27,28] This unique ability of diastolic functional parameters to distinguish between health and disease was eloquently shown by abnormal results on tissue Doppler echocardiography in gene mutation–positive patients with HCM independent of phenotypic expression.[29]

LV Systolic Function. LV systolic function is consistently in the normal range among highly trained athletes.[30] Elite cyclists can have LV ejection fractions lower than normal.[31] Our experience with highly conditioned professional basketball players commonly reveals global LV ejection fractions ranging from 45% to 50%, but supernormal tissue Doppler Sm and normal systolic strain and strain rate measurements.

Systolic strain and strain rate imaging of the left ventricle has been used to distinguish maladaptive from physiologic remodeling of the left ventricle. The absence of reductions in global systolic-longitudinal strain and strain rate supports the use of strain rate imaging to assess the physiologic increase in wall thickness associated with athletic training.[32] Simultaneous measurement of systolic and diastolic strain and strain rate in athletes has not been sufficiently documented at this time. Similarly, the effect of endurance training on deformation mechanics, torsion, and the untwisting rate as components of exercise-induced cardiac remodeling in young athletes needs further investigation.[33] LV systolic torsion and peak early diastolic untwisting rate may be important components of exercise-induced cardiac remodeling.[34] Endurance-trained athletes develop biventricular dilation with enhanced diastolic function, whereas strength-trained athletes develop concentric increases in LV wall thickness with diminished diastolic function.[35] Speckle-tracking echocardiography measures LV systolic and diastolic functions in individuals with structural alterations of the heart from intense physical training. LV untwisting increased with exercise more than LV lengthening or expansion.[36] An exercise-induced increase in LV untwisting rate may enhance early

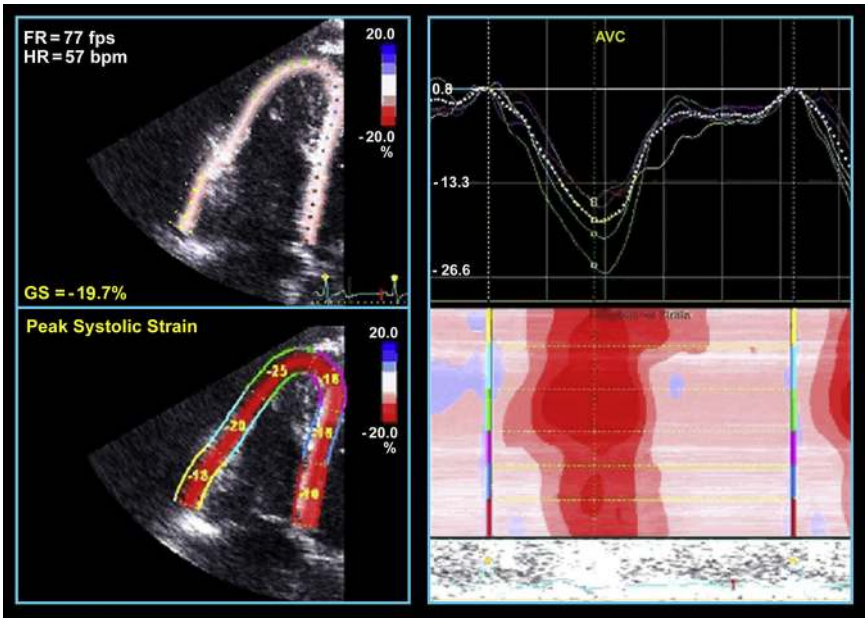

Figure 3 Strain analysis revealing normal peak systolic strain. *GS*, Global strain.

LV diastolic suction, facilitating early LV filling without an increase in left atrial pressure.[37]

Patients with HCM have reductions in longitudinal strain and in the untwisting rate in diastole. The evolving understanding of LV deformation myocardial mechanics is providing incremental information in distinguishing athletic remodeling from disease states such as HCM.

The Right Ventricle

RV remodeling in athletic training is an expectation, because the right ventricle must accept and eject a large volume of blood comparable with that of the remodeled left ventricle. Both the left and right ventricles must augment systolic function to handle the increased blood volume. Endurance-trained athletes have enlarged RV cavities and increased RV wall thickness compared with sedentary controls.[38] RV enlargement parallels LV enlargement in intensely trained athletes.[39] The RV morphologic features in strength-trained athletes do not significantly vary from those in sedentary controls.[40] The morphologic and functional parameters that appear to distinguish endurance- and strength-trained athletes are RV inflow tract diameter, RV end-diastolic area, and tricuspid inflow velocity deceleration time.[40] As expected, in systems that vacillate between normal and abnormal, RV remodeling is heterogeneous across gender, race, and sports discipline.

Physiologic endurance conditioning results in adaptive remodeling of RV structure and function (Video 2; available at www.onlinejase.com). This remodeling may make the distinction from ARVD diagnostically challenging.[41] The echocardiographic features of ARVD reflect the pathologic process of adipose and fibrous infiltration of the RV myocardium, most frequently affecting the RV outflow tract, apex, and inferior basal wall.[42] The distinction between remodeling and RV disease is further distorted by the concern that RV adaptive remodeling associated with prolonged, intense physical training can result in RV pathology. This had led to consideration of possible "exercise-induced RV cardiomyopathy."[43] The potential adverse effects of intense exercise resulting in decreased contractility and altered myocardial substrate–induced arrhythmias[44] beg the question of needing to distinguish between disease states such as ARVD and advanced adaptive remodeling. ARVD has ominous potential, being implicated in 4% to 21% of all cases of SCD.[45] The criterion standard for the diagnosis of ARVD remains poorly defined. Presently, resting measures of RV function such as RV fractional area change, strain, and strain rate are not reflective of RV function reserve, and therefore, low resting RV function as defined by RV fractional area change, S′, strain, and strain rate at rest does not implicate subclinical myocardial damage. RV function may be below normal at rest in highly trained athletes, but there is robust RV functional reserve after provocation with exercise, suggesting that the increased RV and right atrial sizes reflect physiologic remodeling rather than maladaptive changes.[46] Thus, RV contractility, strain, and strain rate at rest do not accurately reflect RV function in highly trained athletes, and exercise testing may be essential to assess RV function. Our need to investigate the impact of high-level training on RV function is related to contradictory data showing that highly trained athletes with RV dilation performing endurance and strength exercises have global strain and strain rate that are preserved or enhanced and that correlate with enhanced S′ and RV fractional area change (Figure 3).[41,47,48] These conflicting data may reflect the heterogeneous response of exercise across variable sports disciplines, volume loading, afterload, and duration of training. Further investigations have identified enhanced RV diastolic function at rest and augmentation of these parameters with intense training. Further investigation of RV diastolic indices, including tissue velocities, strain, and strain rate, at rest and after exercise across a large spectrum of athletes is needed to help distinguish adaptive from maladaptive RV remodeling.

Enhanced contraction of RV free wall segments in athletes compared with regional and global deformation parameters in patients with ARVD may allow the differentiation of physiologic remodeling from disease.[49] Additionally, as stated previously, RV diastolic function, global strain, and response to exercise are key variables separating RV physiologic adaptation from pathology.[50]

Although differences in RV geometric remodeling are observed in endurance- and strength-trained athletes, few reproducible differences in RV cavity deformation or relaxation exist, suggesting that despite remodeling in athletes, RV systolic and diastolic function

Table 3 Relative aortic size predicting rupture

Aortic size index (cm/m^2)	Risk (%)
<2.75	4
2.75–4.25	8
>4.25	20–25

Data from Davies *et al*.[53]

remains normal.[40] It is premature to define "cutoff" values distinguishing remodeling due to athletic training from pathology due to disease. The nonlinear nature of remodeling with heterogeneous phenotypic expression among similarly trained athletes makes this a difficult task. The available data for RV morphologic and functional parameters in relationship to body surface area in athletes are scant. Recent work showed that RV dimensions are greater in athletes than nonathletes. This work provided absolute values for RV morphology and functional parameters in 102 elite endurance-trained athletes and defined the parameters in relationship to body surface area.[41] This is a starting point mandating the need for large, cooperative studies attempting to define normal ranges for athletes across all the various athletic groups.

The Aorta

The remodeling of the aortic root in highly trained athletes is commonly documented. Increased demand resulting in increased stroke volume often results in a larger aortic conduit. Endurance activity results in high-volume aortic flow with modest systolic blood pressure elevation, and strength training results in normal volume aortic flow with profound elevation of systolic blood pressure. There is evidence supporting greater aortic root diameter among strength-trained athletes[51] and refuting data showing the largest aortic dimensions in endurance-trained athletes.[52] The best available measurement in the literature on aortic morphology takes into account aortic dimension and body surface area.[53] The aortic size index is calculated by measuring aortic diameter (centimeters) and dividing by body surface area (square meters). Aortic size index measurements in the athletic population are not well defined. The finding of aortic indexed enlargement should prompt comprehensive evaluation. See Table 3 for guidelines to assess aortic dimensions.

The Atria

A remodeled left atrium is completely normal in the athletic population. Intense athletic training results in increased stroke volume, with subsequent remodeling of all cardiac chambers, including the left and right atria.[54] A more recent study confirmed left atrial remodeling in endurance-trained athletes.[55] The atrial enlargement in trained athletes occurs with preservation of normal LV, RV, left atrial, and right atrial pressures.

Left atrial remodeling in athletes is an expected physiologic adaptive response to exercise training. Left atrial indexed volumes are significantly higher in athletes compared with healthy controls. Doppler tissue imaging is a useful tool to identify improved myocardial diastolic properties in athletes, and speckle-tracking echocardiography elucidates the role of the left atrium in athletic heart remodeling.[56] Left atrial strain and strain rate by two-dimensional speckle-tracking are indices of left atrial function that facilitate distinction of physiologic and pathologic remodeling. Left atrial myocardial deformation is significantly impaired in patients with HCM compared with athletes and healthy controls.[57]

EXERCISE TESTING

Screening stress testing is not useful in asymptomatic patients. LV systolic function response to exercise is more robust in healthy athletes compared with patients with HCM.[58] Maximum oxygen uptake is increased in athletes as a result of upregulation of cardiopulmonary delivery of oxygen and skeletal muscle use of oxygen. The major difference between athletes and nonathletes is the ability to increase cardiac output. This is attributable to enhanced stroke volume.[59] Doppler tissue imaging measures have demonstrated augmentation of systolic and diastolic functions in elite athletes.[60]

SEX

Athletic cardiac remodeling exhibits no gender bias; it occurs in both sexes and is of similar but not equivalent magnitude in male and female athletes. The degree of individualized physiologic remodeling is less pronounced in women matched to men, even when corrections are made to take account of slighter lower body surface areas in women.[61,62]

RACE

Race is an important element of cardiac remodeling, with individual differences in wall thickness between white and black athletes. This distinction transcends sex, with black female athletes having greater wall thickness and LV mass than white female athletes.[63] Black athletes show a more prominent pattern of LV remodeling compared with whites, characterized by greater increases in LV wall thickness, mass, and relative wall thickness but similar cavity size and volume.[64] Individual differences in the degree of wall thickening suggest an indefinite etiologic factor associated with the black race that augments physiologic wall thickening in response to the volume burden associated with intense athletic training. Athletes of all races are expected to have preservation of normal or hypernormal cardiac myocyte function despite morphologic changes.

MULTIMODALITY IMAGING IN ATHLETE'S HEART

Echocardiography provides a robust understanding of cardiac pathophysiology. High temporal resolution enables the assessment of myocardial function at rest and during exercise regionally and globally. Echocardiography is the best imaging modality because it allows the simultaneous evaluation of cardiac morphology and diastolic function. This allows individualization of the global morphophysiologic state.

Cardiac magnetic resonance imaging (MRI) has excellent spatial resolution and image quality that is not influenced by body habitus, permitting precise measurements of cardiac chamber size, myocardial mass, and systolic function. This has particular benefit for the irregularly shaped right ventricle.[65] Cardiac MRI has incremental value in distinguishing athletic heart and HCM in selected cases because of its superiority in identifying segmental increase in LV wall thickness in the anterolateral free wall and apex.[66] In the severe phenotypic expression of ARVD, all imaging modalities are likely to identify the disease.[67] An important role of cardiac MRI in the athletic population lies in its ability to detect early and subtle cases of ARVD that are otherwise insensitive to diagnosis. Cardiac MRI can uniquely detect regional and diastolic dysfunction, which may represent early manifestations of ARVD.[68] Cardiac MRI also allows the detection of LV involvement in

ARVD[69] and is a useful technique for the noninvasive identification of anomalous coronary arteries and their anatomic course.[70]

Radionuclide ventriculography attempts to provide measures of ventricular systolic function that do not rely on geometric assumptions and has been used to assess function with exercise. This imaging modality is limited by cost and radiation exposure and has little value given the alternative modalities for measuring systolic function.

Positron emission tomography imaging has been used to evaluate perfusion reserve in athletes. Supine bicycle exercise with positron emission tomographic scanning has demonstrated that increased myocardial mass does not impede blood supply in athletes. Positron emission tomography through tissue characterization in the future may allow the identification of subtle changes in myocardial and interstitial composition, ascertaining whether the morphologic changes observed in athletes are physiologic or pathologic.[71]

Cardiac computed tomography allows the evaluation of coronary artery disease and possesses superb spatial resolution for anatomic definition. Cardiac computed tomography has been limited to use in older athletes to exclude coronary artery disease. The amount of radiation exposure limits its use to assess cardiac function.

PARTING THOUGHTS

The accuracy of Doppler echocardiography is time tested and validated. Doppler echocardiography allows one to sensitively and specifically distinguish adaptive from maladaptive remodeling. It is clinically effective and cost effective. Echocardiography is available throughout the world and allows the simultaneous assessment of morphology and physiology.

CASE EXAMPLES

The first example is of a National Basketball Association player who presented for a second opinion because he was disqualified from sports participation. His disqualification was based on a diagnosis of LV noncompaction cardiomyopathy. The diagnostic predicament was tackled with an integrated consideration of history, 12-lead electrocardiography, and echocardiography. The personal and family histories were unremarkable. The 12-lead electrocardiogram revealed increased voltage and early repolarization. These electrocardiographic changes were compatible with an athletically trained black athlete. The echocardiogram was intriguing (Figures 1–3, Videos 1–6; available at www.onlinejase.com). The morphologic changes were obvious, with remodeling and enlargement of all cardiac chambers, increased LV wall thickness, and evidence of marked apical trabeculations and chords and a bilayered myocardium. The calculated LV ejection fraction was 55%. In this case, the morphologic changes are marked and give pause for the physician trying to separate a healthy heart from a disease state.

This patient had cardiac remodeling with increased wall thickness (12 mm) and enlargement of all cardiac chambers. Tissue Doppler echocardiography revealed supernormal early diastolic relaxation ($e' > 17$ cm/sec) and supernormal peak systolic tissue velocity ($Sm > 10$ cm/sec). Additionally, global longitudinal strain and strain rate were normal. The patient achieved 22 metabolic equivalents on the Bruce protocol.

Integrating the patient's morphology, physiology, myocardial mechanics, and exercise testing results led to a conclusion of athletic heart superimposed on LV noncompaction morphology with normal LV systolic function, the latter being a morphologic finding and not representative of a disease state. The patient was cleared to play professional basketball with a recommendation for follow-up in 1 year.

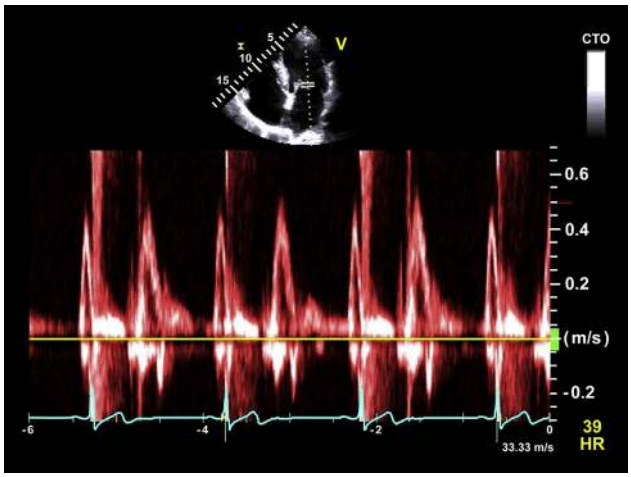

Figure 4 Pulsed-wave Doppler of mitral inflow. The heart rate was 39 beats/min, and there was a normal period of diastasis. Despite intense athletic training, this 74-year-old man had less proficient diastolic filling and a dominant A wave.

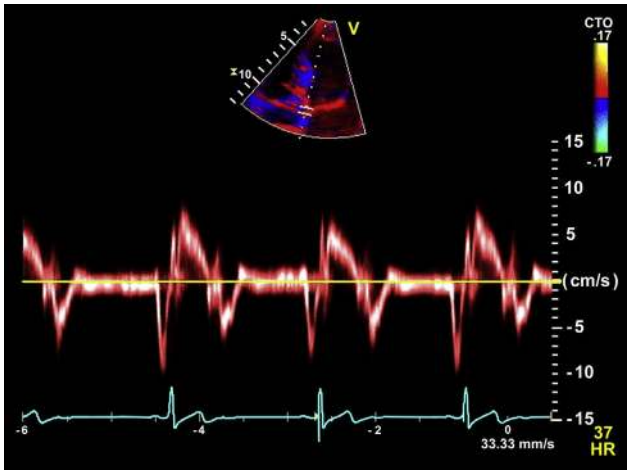

Figure 5 Medial annular tissue Doppler with a grade 2/4 diastolic pattern but normal LV filling pressure ($E/e' = 7$). The remodeled left atrium has preserved LV filling pressure, consistent with athletic heart.

The second example, which shows the distinction between athletic training–induced cardiac remodeling and structural heart disease, is of a 74-year-old white man referred for evaluation of a cardiomyopathy and the need for an implantable cardioverter-defibrillator. The patient had an episode of fatigue on a 40-mile bike ride. A previous cardiac catheterization test revealed normal coronary arteries. The personal history revealed that the patient rode his bike an average of 40 mi/d and recently had ridden from the west coast to the east coast of the United States in 2 months. The patient's family history was unremarkable. Twelve-lead electrocardiography revealed marked sinus bradycardia with heart rates ranging from 30 to 39 beats/min, increased voltage, and early repolarization.

Echocardiography revealed obvious chamber enlargement (Figures 4–6, Videos 7–11; available at www.onlinejase.com). LV and RV systolic function appeared depressed visually. No significant valvular abnormalities were identified. Diastolic function revealed that e' and E/e' were normal, as was peak annular systolic tissue velocity. Calculated LV ejection fraction and RV fractional area change

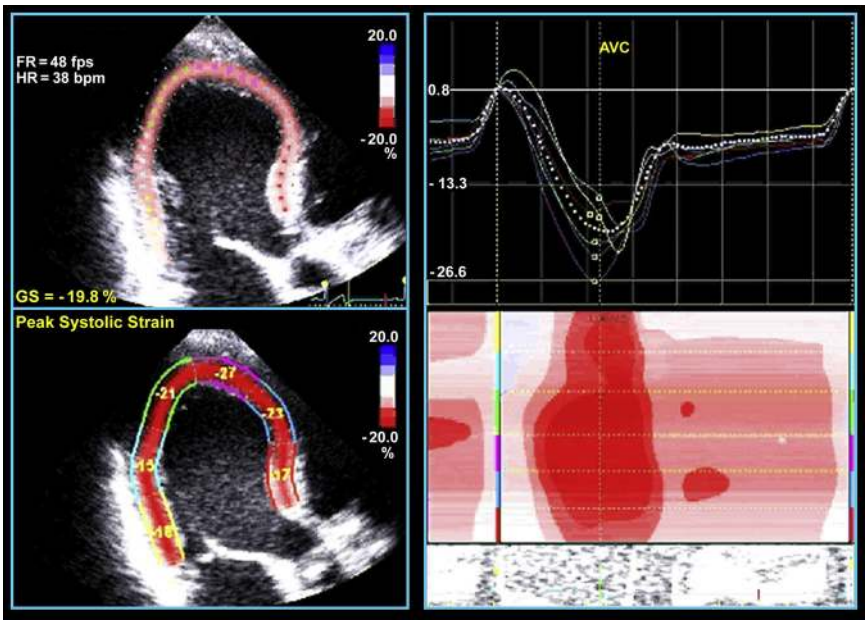

Figure 6 Strain analysis revealing normal mechanical function with peak systolic strain equal to −19.8%. *GS*, Global strain.

were normal, as were the results of strain analysis. This 74-year-old man reached a workload of 19 metabolic equivalents on exercise testing. Echocardiographic analysis demonstrated extreme cardiac remodeling from chronic, intense physical training. The left ventricle raised concern for dilated cardiomyopathy, and the RV dimensions raised concern for RV cardiomyopathy. The analysis of systole, diastole, LV and RV mechanics, and stress testing identified physiologic remodeling of the left and right ventricles.

These two examples embody the degree and magnitude of cardiac remodeling associated with intense physical training. Although morphologic changes associated with intense exercise training can create a diagnostic conundrum when attempting to distinguish athletic remodeling from pathologic structural heart disease, functional myocardial imaging generally permits precise assessment of function and separation of health from disease.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2014.06.008.

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STATE-OF-THE-ART REVIEW

Sudden Cardiac Death in Athletes

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CME/MOC Objective for This Article: Upon completion of this activity, the learner should be able to: 1) describe the epidemiology of SCD in the athlete population; 2) discuss the relevant elements of a pre-participation cardiovascular screening examination for risk stratification of competitive athletes; and 3) identify components of an emergency action plan for schools and organizations hosting athletic events or training facilities.

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Sudden Cardiac Death in Athletes

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ABSTRACT

Sudden cardiac death is a tragedy at any age and under any circumstances but is perhaps most tragic when it claims the life of the athlete, the individual who epitomizes health and a healthy lifestyle. Sports cardiologists from around the world have worked to quantitate the incidence of sudden cardiac death (SCD) in the athlete, to identify risk factors, to develop pre-participation screening tools, and to formulate plans to deal with on-field SCD. Progress has been made, but much remains to be done in order to make both competitive and recreational sports safer for both patients with known cardiac disease and athletes without known or suspected cardiac abnormalities. (J Am Coll Cardiol HF 2018;6:30–40) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Sudden cardiac death (SCD) in an apparently healthy athlete is a tragic event, counterintuitive to the common association between athletic activity and good health. These tragedies are highly publicized and generate considerable attention in the local community, which may then commit significant financial resources to prevent future events. The medical community, in turn, looks to the cardiac care team for guidance on the identification of athletes at risk, primary and secondary prevention strategies, and treatment.

Addressing this issue is complex as athletes come in all shapes, sizes, and ages. Sports can require various levels of cardiac performance, even within the same sport. The position played, the training required, and the environmental stresses make each athlete an individual study of risk and benefit. Data for athletes and SCD come from disparate sources, and expert consensus drives many published recommendations. This review informs the provider community of the current state of knowledge regarding the athletes at risk for SCD.

INCIDENCE OF SUDDEN CARDIAC DEATH

The true incidence of SCD in an athletic population is controversial. Estimates from studies in the United States and Europe are all complicated by various methodological issues (**Table 1**). The basis of these discrepancies revolves around what is included in the numerator (number of athletes who have experienced SCD) and the denominator (number of athletes at risk) of these equations. Some studies have included only events that resulted in death (1–7), whereas others also include those that survive sudden cardiac arrest (SCA) (8–12). Methods relying on media reports, passive registries, and catastrophic insurance claims have been used predominantly to develop incidence reports which may underestimate SCD incidence. Drezner et al. (11) examined a population of Minnesota high school athletes over a 10-year period, using media reports from the Parent Heart Watch database and found 6 cases of SCD compared to only 1 case identified by using catastrophic insurance claims. The variability in reporting among National Collegiate Athletic Association (NCAA) athletes was demonstrated by Harmon et al. (7), who identified SCD from 2003 to 2013 through 3 different sources: 1) the NCAA Resolutions List; 2) the Parent Heart Watch database; and 3) NCAA insurance claims. Media database reports identified 70% of the total SCD cases, whereas insurance claims captured only 11% of cases.

Sudden cardiac death is a relatively infrequent event, and to study it, large, stable populations must be observed over a period of many years to account for random variability in death rates. Corrado et al. (2) published one of the first large scale studies of sudden cardiac death in athletes in the Veneto region of Italy. Over the final period of the study (2003 to 2004), the incidence of SCD was 0.4 per 100,000 person years (n = 1 death), whereas in the initial period (1979 to 1980), it was 3.6 per 100,000 person years (n = 8 deaths) with an average of approximately 2 deaths per year over the entire 26-year study period. This was similar to findings in an Israeli study by Steinvel et al. (9) over a 30-year time frame with a cumulative incidence of 2.6 per 100,000 person-years (n = ~1 death/year). However, there was a noted spike in deaths during their 30-year study period from 1995 to 1996, with an incidence of 8.4/100,000 person-years, whereas 2 periods (1989 to 1990 and 1993 to 1994) had zero deaths.

A consistent finding across studies is that male athletes have a 3 to 5 times higher incidence of SCD

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

DCM = dilated cardiomyopathy

HCM = hypertrophic cardiomyopathy

SADS = sudden arrhythmic death syndrome

SCA = sudden cardiac arrest

SCD = sudden cardiac death

than female athletes (1,13). Data from NCAA athletes also indicate that black athletes (incidence rate ratio of 3.2 compared to white athletes) and in particular Division I basketball players (1:5,200 athlete-years for all males and 1:4,380 athlete-years for black males) have a markedly higher incidence of SCD (7). Recognizing heterogeneity may help with efforts to target preventive strategies for groups with the highest risk.

The burden of SCD in athletic individuals must be considered in context of the risk of SCD in the general population. Studies indicate that the physical endeavor of sport activity and training poses a 2.4 to 4.5 increased risk of SCA and SCD relative to that in nonathletes and recreational athletes (2,10,14). Although sporting activity appears to increase the relative risk of SCD, the absolute number of cases is larger in the nonsporting population. Over the 10-year period of the Oregon Sudden Unexpected Death Study, there were 1,184 nonsport-associated SCA compared to 63 sport-associated SCA for patients 35 to 65 years of age (15). There are an estimated 201,286 cases of SCA/SCD across the general population in the United States annually (16), and, although extrapolation from the Oregon experience may not be entirely justified, the absolute number of SCD cases attributable to athletic activity will be a relatively small number when considering issues of population health.

PRIMARY PREVENTION AND SCREENING STRATEGIES

A pre-participation evaluation (PPE) prior to competing in athletics has been recommended by multiple societies (17–22) to identify or raise the suspicion of cardiovascular abnormalities that could potentially result in SCD on the athletic field (17). The appropriate components of the PPE are a subject of significant controversy and vary by country, league, and level of competition.

HISTORY AND PHYSICAL EXAMINATION. The American Heart Association (AHA) has published guidelines for the pre-participation screening of competitive athletes, which consist of a 14-point history and physical examination (23). The 14-point PPE is a Class I recommendation in the most recent Eligibility and Disqualification Recommendations for Competitive Athletes study published by the American College of Cardiology (ACC)/AHA (17). The Pre-Participation Physical Evaluation Monograph, 4th edition (PPE-4), is a joint project of 6 medical organizations whose members are intimately involved in pre-participation assessments (21) and is endorsed by the AHA (23) (**Table 2** compares the AHA 14 points with the PPE-4 elements). Despite the fact that these and similar recommendations have been in place for decades, studies indicate the general lack of awareness and incorporation into many state and school district policies in the United States (24–28).

The PPE medical history questions were developed through expert consensus and have not been scientifically validated in a prospective study. A systematic review/meta-analysis from Harmon et al. (7) reported a sensitivity and specificity for the detection of serious cardiac abnormalities to be 20% and 94%, respectively, for the history and 9% and 97%, respectively, for the physical examination. This likely reflects a high number of initial positive responses (24% to 68%) reported by high school and college athletes on questionnaires (29–31). Although initial responses on the PPE form are meant to be reviewed by a physician to determine if further evaluation is warranted, a study from Fudge et al. (31) suggested that 46% of initial positive responses necessitated further evaluation even after physician review. The AHA 14-point PPE and the PPE-4 monograph are considered the bases of any PPE and efforts to standardize them across institutions and states in the United States are crucial to their success.

ELECTROCARDIOGRAPHY. The addition of an electrocardiography (ECG) to the standard PPE has been mandated in Italy (2) and Israel (9) and has been recommended by the European Society of Cardiology (20) and International Olympic Committee (32). Data suggest the sensitivity of the ECG to detect underlying cardiovascular abnormalities that could place the athlete at risk of sudden cardiac death is superior to that of the history and physical examination (7). However, the addition of a resting ECG to screening protocols has not been evaluated in a prospective study. Data from Israel (9), which mandates ECG screening, and Minnesota (8), where ECG screening does not take place, suggest rates of SCD similar to that of Italy after the implementation of their mandated ECG screening program (9). In the United States, the issue of ECG screening in the collegiate athlete has been a topic of discussion in the lay press, although no mandate has emerged from the debate (22,33–35). Unfortunately, given the logistics and including financial costs and sheer volume of participants needed, a randomized, controlled trial of screening to prevent sudden cardiac death in the athlete is likely unrealistic.

First Author (Ref. #)	Year	Incidence (per Athlete-Person Yrs)	Total Number of Cases	Definition(s)	Time Frame of Events	Population	Collection Method(s)	Age Range (yrs)	Study Period
Van Camp et al. (7)	1995	1/281,000	107	SCD	C/T	17 U.S. high school and college sports (excluded intramural, club, and PE classes)	Retrospective from National Center for Catastrophic Sports Injury Research database and media database	17–24	1983–1993
Corrado et al. (2)	2006	1/115,000 over the final 11 yrs (1/53,000 over the total period)	55	SCD	All	Veneto region, Italy	Prospective registry	12–35	1979–2004
Maron et al. (8)	2009	1/103,000	22	SCA+D	All	MN high school, collegiate, and professionals	Catastrophic Insurance Records; U.S. National Registry of Sudden Death in Athletes; NCAA website/communications; public records	12–31	1985–2007
Maron et al. (8)	2009	1/164,000	1,049	SCA+D	All	U.S. competitive organized team or individual sports (intramural/recreational excluded)	U.S. National Registry of Sudden Death in Athletes (media reports, directly submitted, NCCSIR, NHLBI)	8–39	1980–2006
Holst et al. (3)	2010	1/83,000	15	SCD	C/T	Competitive athletes	Denmark nationwide death certificates	15–35	2000–2006
Solberg et al. (4)	2010	1/117,000	23	SCD	All	During, or in connection with, physical activity	Retrospective Norwegian Cause of Death Registry, medical records, and autopsy reports from hospitals and clinics	15–34	1990–1997
Steinvil et al. (9)	2011	1/39,000	24	SCA+D	All	Israel Sport Law ("individuals who engage in sportive activity at any level of physical endurance")	Media reports	12–44	1985–2009
Marijon et al. (10)	2011	1/102,000	50	SCA+D	C/T	Competitive athletes in France: participated in an organized sports program (team or individual) that required regular competition and training (excludes intramural sports)	Prospective population based using EMS responding to cardiac cases; media reports	10–35	2005–2010
Roberts and Stovitz (5)	2013	1/417,000	4	SCD	C/T	MN State High School League	Catastrophic Insurance Records	12–19	1993–2012
Drezner et al. (11)	2014	1/71,000	13	SCA+D	All	MN high school athletes	Public Media Reports (Parent Heart Watch)	14–18	2003–2012
Maron et al. (6)	2014	1/63,000	64	SCD	All	NCAA athletes	U.S. National Registry of Sudden Death in Athletes; NCAA Memorial Resolutions List	17–26	2002–2011
Harmon et al. (7)	2015	1/54,000	79	SCD	All	NCAA athletes	1) NCAA Resolutions List; 2) Parent Heart Watch database; and 3) NCAA insurance claims.	18–26	2003–2013
Harmon et al. (12)	2016	1/101,000 SCD 1/67,000 SCD+SCA	69 SCD 104 SCA+SCD	SCD SCA+SCD	All	High school athletes from 7 states (CA, FL, MN, NJ, OH, TN, and TX)	Parent Heart Watch database	14–18	2007–2013

C/T = competition/training (defined as during or within 1 h of cessation of activity); EMS = emergency medical service; NCAA = National Collegiate Athletic Association; NCCSIR = National Center for Catastrophic Sports Injury Research; NHLBI = National Heart, Lung, Blood Institute; PE = physical education; SCA = sudden cardiac arrest; SCD = sudden cardiac death.

CAUSES OF SUDDEN CARDIAC DEATH

The cardiac abnormalities contributing to SCD in athletes ≤35 years of age generally fall into 3 categories: electrical, acquired, and structural cardiac abnormalities (**Figure 1**). Most of these abnormalities are inherited cardiac disorders that may be quiescent but can predispose the athlete to SCD primarily through ventricular arrhythmia (13). Primary, inherited electrical cardiac abnormalities were implicated in ≤5% of confirmed SCD events in the U.S. Registry (8) and <4% in NCAA athletes (6,7), and 0% were identified in studies from the United Kingdom (36) and Australia and New Zealand (37). Acquired

AHA Recommendations	Pre-Participation Physical Evaluation
Medical history*	
Personal History	Heart Health Questions About You
1. Chest pain/discomfort/tightness/pressure related to exertion	6. Have you ever had discomfort, pain, tightness, or pressure in your chest during exercise?
2. Unexplained syncope/near syncope†	5. Have you ever passed out or nearly passed out DURING or AFTER exercise?
3. Excessive and unexplained dyspnea/fatigue or palpitations, associated with exercise	12. Do you get more tired or short of breath more quickly than your friends during exercise? 10. Do you get lightheaded or feel more short of breath than expected during exercise? 7. Does your heart ever race or skip beats (irregular beats) during exercise?
4. Prior recognition of a heart murmur 5. Elevated systemic blood pressure	8. Has a doctor ever told you that you have any heart problems? If so, check all that apply: ☐ High blood pressure ☐ A heart murmur ☐ High cholesterol ☐ A heart infection ☐ Kawasaki disease Other: _____
6. Prior restriction from sports	1. Has a doctor ever denied or restricted your participation in sports for any reason?
7. Prior testing for heart disease, ordered by a physician	9. Has a doctor ever ordered a test for your heart? (For example, ECG/EKG, echocardiogram) 11. **Have you ever had an unexplained seizure?**
Family History	Heart Health Questions About Your Family
8. Premature death (sudden and unexpected or otherwise) before 50 yrs of age attributable to heart disease ≥1 relative	13. Has any family member or relative died of heart problems or had an unexpected death before age 50 (including drowning, unexplained car accident, or sudden infant death syndrome)?
9. **Disability from heart disease in a close relative <50 yrs of age**	
10. Hypertrophic or dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac condition in family member	14. Does anyone in your family have hypertrophic cardiomyopathy, Marfan syndrome, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia? 15. **Does anyone in your family have a heart problem, pacemaker, or implanted defibrillator?** 16. **Has anyone in your family had unexplained fainting, unexplained seizures, or near drowning?**
Physical examination	Physical examination
11. Heart murmur‡	a. Heart Murmurs (auscultation standing, supine, with or without Valsalva) Location of point of maximal impulse
12. Femoral pulses to exclude coarctation	b. Pulses Simultaneous femoral and radial pulses
13. Physical stigmata of Marfan syndrome	c. Appearance Marfan stigmata (kyphoscoliosis, high-arched palate, pectus excavatum, arachnodactyly, arm span >height, hyperlaxity, myopia, MVP, aortic insufficiency)
14. Brachial artery blood pressure (sitting position)§	d. Blood pressure

The table compares the 14-element American Heart Association recommendations for pre-participation cardiovascular screening of competitive athletes and the pre-participation physical evaluation monograph; differences are shown in **bold**. *Parental verification is recommended for high school and middle school athletes. †Judged not to be of neurocardiogenic (vasovagal) origin; of particular concern when occurring during or after physical exertion. ‡Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both the supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction. §Preferably taken in both arms. Reproduced with permission from Hainline et al. (78).

AHA = American Heart Association; ECG = electrocardiogram; EKG = electrocardiogram; MVP = mitral valve prolapse; PPE-4 = Pre-Participation Physical Evaluation Monograph, 4th edition.

abnormalities such as commotio cordis, which is increasingly reported in the United States and worldwide (38,39); myocarditis, which may have multiple causes (40); and environmental factors and performance-enhancing drugs have been linked with SCD in athletes (41,42). Anomalous coronary artery origins, particularly a coronary artery originating from the wrong aortic sinus, is a frequent cause of SCD, ranging from 7% to 17% of athlete cases (8,36,43). Atherosclerotic coronary artery disease is an uncommon but recognized cause of SCD in young athletes (8,13,37), whereas it becomes the dominant mechanism in older athletes (>60% of cases in athletes >35 years of age) (10,15,44–46).

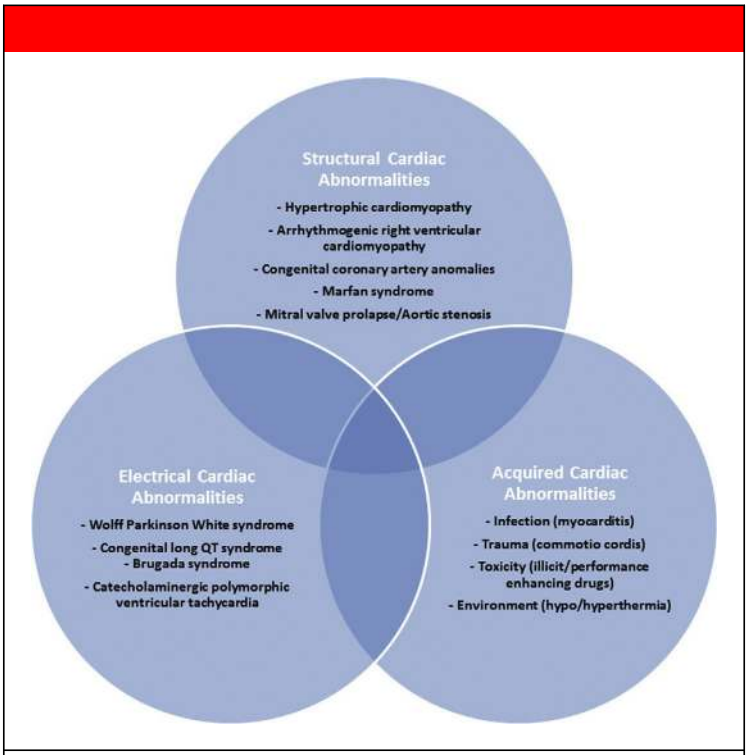
Inherited structural cardiac conditions comprise most of the structural abnormalities resulting in SCD

in the young athletic population. Hypertrophic cardiomyopathy (HCM) is often cited as the most common cause of SCD in young competitive athletes, accounting for 36% of confirmed causes of SCDs in the U.S. National Registry of Sudden Death in Athletes (8,18), with a significant number of SCD cases labeled as "possible HCM" (8%). The prevalence of HCM in the general population is approximately 1:500 (0.2%) (47) but may in fact be less common (<0.07%) in athletes (48,49). More contemporary studies are starting to question the proportion of SCD attributed to HCM. A study from the United Kingdom found only 12% of SCDs in athletes was attributable to definitive HCM, with 25% of SCDs exhibiting idiopathic left ventricular hypertrophy (36). A prospective study of SCD among children and young adults conducted in Australia and New Zealand from 2010 through 2012 attributed only 6 of 54 cases (11%) of HCM during or post-exercise, whereas 20 were unexplained (37%) (37). Alpert et al. (50) condensed several published studies to generate an estimated risk of SCD for athletes due to HCM at 0.03% to 0.1%, which is comparable to contemporary published mortality rates in the overall HCM population (51).

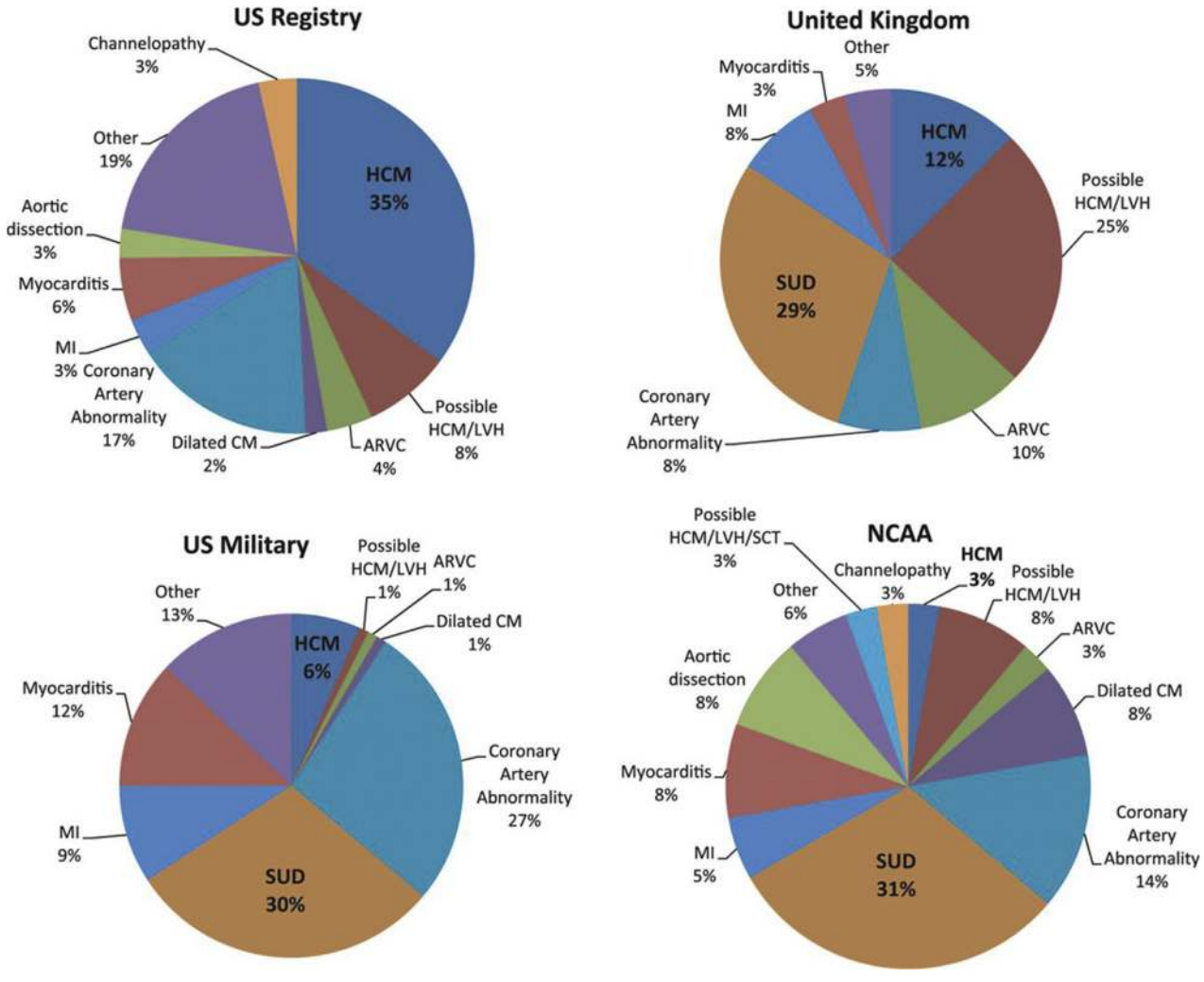
Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty replacement of the RV myocardium with variable disease expression that can increase risk of SCD, notably during exertion (52). ARVC is the most common cause of SCD (24%) in athletes in the Italian registry from the Veneto region (13). It is also more common in the United Kingdom (10% among those ≤35 years of age) (36) than in the United States, including cohorts from the U.S. Registry of Sudden Death in Athletes, NCAA athletes, and U.S. military (6,8,43,53,54). The role that exercise may play in disease progression of individuals with genetic ARVC has evolved recently. In a study from James et al. (55), endurance athletes with desmosomal mutations developed symptoms at a younger age (30 vs. 41 years of age) and were more likely to develop ventricular tachycardia and ventricular fibrillation and heart failure. In a separate study from Sawant et al. (56), gene-elusive, nonfamilial ARVC was associated with more intense exercise prior to presentation and were more likely to be endurance athletes particularly among those presenting at <25 years of age. Unlike most other cases of cardiomyopathic processes, subjects who have possible or borderline cases of ARVC and probably even genotype-positive, phenotype-negative cases should not participate in competitive sports or even moderate to intense recreational exercise (Class III) (57).

Dilated cardiomyopathy (DCM) is another potential cause of SCD in athletes. Mild forms of DCM can be difficult to distinguish from "athlete's heart." Although a mildly reduced ejection fraction (EF; 40% to 50%) is not typical of "athlete's heart," it has been noted in several observational studies (58–60), particularly associated with increased left ventricular dimensions. These studies have also noted that the EF "augments normally" (59) or becomes "hyperdynamic" (60) with exercise, when observed by stress echocardiography. This adaptation likely reflects increased cardiac output, as attained primarily through increased stroke volume necessary to achieve the athletic prowess of a competitive athlete. As such, it would be anticipated that these subjects' ejection fraction would increase normally with exercise (i.e., by stress echocardiography) and also be reflected in other objective measurements of fitness (i.e., V_{O_2}max) (61). Contemporary studies of myocardial contractile reserve as reflected by EF are needed to better classify the degree of augmentation by stress imaging that provides the best sensitivity and specificity for differentiating a mild DCM from the physiological adaptations of "athlete's heart."

Several studies have noted a higher than expected incidence of "morphologically normal hearts" than previously suspected (36,43,62). These cases are commonly referred to as sudden arrhythmic death syndrome (SADS), autopsy-negative SCD, or sudden



Reproduced with permission from Chandra et al. (79).

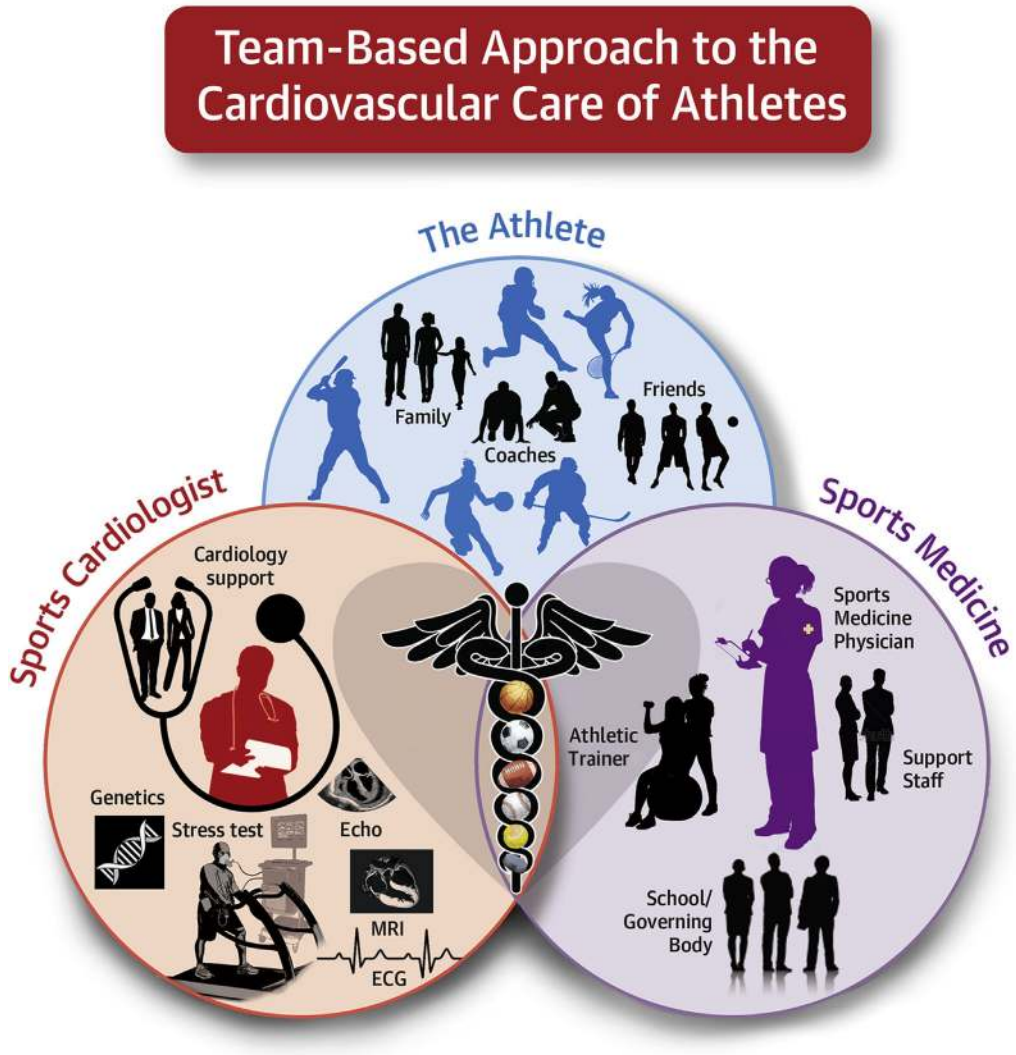


ARVC = arrhythmogenic cardiomyopathy; CM = cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; MI = myocardial infarction; NCAA = National Collegiate Athletic Association; SCT = sickle cell trait; SUD = sudden unexplained death. Reproduced with permission from Harmon et al. (43).

unexplained death. Studies from the United Kingdom (36,62), NCAA (7,43), and U.S. military (53,54) indicate that SADS may be the most common finding in postmortem assessment (**Figure 2**). This group may in fact be comprised of a significant number of primary electrical disorders or channelopathies (63,64) that may be identified best by molecular autopsy. These are often difficult diagnoses to establish postmortem, unless specific protocols are followed to preserve material for genetic testing (64). In an ambitious study from Australia and New Zealand (37), all SCDs among children and young adults 1 to 35 years of age were prospectively studied from 2010 to 2012, with inherited cardiomyopathies representing 16% of the cases. Forty percent of the cases were unexplained at autopsy, with subsequent genetic analysis identifying pathogenic or probably pathogenic gene variants in 27%.

RISK STRATIFICATION AND RETURN TO PLAY

The individual with identified cardiac disease presents a challenge to the cardiac care team, the league/club, the athlete and their loved ones. The decision to disqualify or restrict an athlete is complex. The AHA/American College of Cardiology Foundation published scientific statements on eligibility and disqualification recommendations for



Multidisciplinary care of athletes focused on athlete-centered care ("Athlete Care Team") in the evaluation and management of athletes at risk of sudden cardiac death.

competitive athletes with cardiovascular abnormalities in 1985 (65), 1994 (66), 2005 (67), and 2015 (68). These documents inform the medical community as to consensus strategies to protect the athlete from harm while being mindful not to unnecessarily remove individuals from a healthy athletic lifestyle or competitive sports.

Although risk stratification for SCD exists for many cardiomyopathic processes within a general population setting, there is less to guide the clinician with regard to risk stratification of the asymptomatic athlete who may have cardiac disease. This area of uncertainty is particularly evident in the 2015 AHA/ACC Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities, where a significant portion of the document(s) contains recommendations that carry Class II recommendations, where clinical and scientific uncertainty remain (68). Eligibility and disqualification criteria have been based almost exclusively on expert consensus, with limited data from a few, small observational registries primarily

with congenital long-QT syndromes and implantable defibrillators (69–73). This underscores the lack of studies in this unique population, particularly asymptomatic athletes, and the need for future research to better identify risk stratification paradigms that may help quantify the risks of participating in competitive athletics with certain cardiovascular disorders. Given these levels of uncertainty, participation in competitive athletics with a cardiovascular disorder should be a shared decision-making process (74) between the physician(s), the athlete, the family, and the school and/or governing body (**Central Illustration**).

EMERGENCY ACTION PLANS

Even with the best of primary and secondary prevention, SCD will occur, placing not only athletes but also event spectators at risk. The response to a sudden cardiac arrest at any athletic venue is an important component of any discussion of SCD in athletes. An athlete experiencing cardiac arrest can be effectively resuscitated with prompt recognition, rapid cardiopulmonary resuscitation, and application of an automated external defibrillator (AED). A study from Weisfeldt et al. (75) demonstrated that prompt application of an AED is associated with greater likelihood of survival (odds ratio: 1.75; 95% confidence interval: 1.23 to 2.50; $p < 0.002$), with the highest survival to hospital discharge noted in places of recreation (49%) (75). An effective EAP necessitates the integration of adequate training (including coaches), rapid access to functioning AEDs, and effective communication with local EMS as well as the regular review and rehearsal of the emergency action plan (EAP) (76,77).

CONCLUSIONS

Sudden cardiac death in the athlete is a rare but catastrophic event for families, teams, leagues, and communities. The cardiac care team needs to be informed about strategies to identify those at risk and to respond to events. Although there is a significant body of knowledge addressing SCD in the athlete, much more needs to be done. Better epidemiology is needed to identify those at highest risk, and longitudinal registries should follow participants who have specific abnormalities. Observational or randomized trials need to be performed to test hypotheses regarding some of the alternative management strategies with clinical equipoise. It is the role of the professional to understand the issues, inform the athletes at risk, and protect those at highest risk.

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