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Turkish Journal of Pediatric Disease

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Official Journal of Ankara City Hospital, Child Hospital

Türkiye Çocuk Hastalıkları Dergisi
Turkish Journal of Pediatric Disease

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Türkiye Çocuk Hastalıkları Dergisi, Ankara Şehir Hastanesi Çocuk Hastanesi'nin açık erişimli bilimsel yayındır. Dergi bağımsız, tarafsız ve çift-kör hakemlik ilkelerine uygun olarak yayınlanır. Dergi iki ayda bir yayınlanmaktadır (Ocak Mart, Mayıs, Temmuz, Eylül, Kasım)

Türkiye Çocuk Hastalıkları Dergisi'nin yayın dili İngilizcedir. Ancak dergi değerlendirme için Türkçe ve İngilizce yazılar da kabul edilmektedir. Ancak Türkçe yazılmış makalelerin yazarlarının yazının kabul edilemesi durumunda yayınlanmak üzere dergiye yazının İngilizce versiyonunu yüklemeleri gerekmektedir.

Türkiye Çocuk Hastalıkları Dergisi'nde orijinal makale, derleme, olgu sunumu, editöryal, çalışma yöntemi, kısa rapor, kitap incelemeleri, biyografiler ve editöre mektup yayınlanmaktadır. Ayrıca pedatrik cerrahi, diş hekimliği, halk sağlığı, genetik, çocuk ve ergen psikiyatrisi ve hemşirelik konularında makaleler yayınlanabilir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir.

Türkiye Çocuk Sağlığı ve Hastalıkları Dergisi TÜBİTAK/ULAKBİM Türk Tıp Dizini, EBSCOhost Research Databases ve Türkiye Atıf Dizini tarafından indekslenmektedir.

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Yazarların Bilimsel ve Hukuki Sorumluluğu

Yazarlar Türkiye Çocuk Hastalıkları Dergisi'ne bir yazı gönderirken, yazıların telif haklarını Türkiye Çocuk Hastalıkları Dergisi'ne devretmiş olmayı kabul ederler. Yayınlanmamak üzere reddedilirse veya herhangi bir sebepten yazı geri çekilirse telif hakkı yazarlara geri verilir. Türk Türkiye Çocuk Hastalıkları Dergisi'ne ait Telif Hakkı Devri ve Yazarlık Formları (https://dergipark.org.tr/tr/pub/tchd adresinden indirilebilir). Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayınlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir.

The Turkish Journal of Pediatric Disease is an open access and a scientific publication journal that is published from the Ankara City Hospital, Children's Hospital. The journal is published in accordance with independent, unbiased, and double-blind peer review principles. The journal is published bimonthly (January, March, May, July, September, November)

The publication language of Turkish Journal of Pediatric Disease is English. However, the journal welcomes manuscripts both in Turkish and English for the evaluation. The authors of articles who had manuscript in Turkish are required to provide an English version of their accepted article before the publication.

In the Turkish Journal of Pediatric Disease original articles, reviews, case reports, editorials, short reports, book reviews, biographies and letters to the editor are also published in the journal. Besides if related with pediatrics, articles on aspects of pedatric surgery, dentistry, public health, genetics, pshyciatrics and nursery could be published.

Manuscripts submitted to the Turkish Journal of Pediatric Disease will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field, in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

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Derginin yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (WAME)), Yayın Etiği Komitesi (Committee on Publication Ethics (COPE)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)), Bilim Editörleri Konseyi (Council of Science Editors (CSE)), Avrupa Bilim Editörleri Birliği (EASE) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO) (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice)) uygundur.

Yazıların yayına kabulü için en önemli kriterler özgünlük, yüksek bilimsel kalite ve atıf potansiyelidir. Değerlendirme için gönderilen yazılar daha önce elektronik veya basılı bir ortamda yayınlanmamış olmalıdır. Dergi, değerlendirilmek üzere başka bir dergiye gönderilen ve reddedilen yazılar hakkında bilgilendirilmelidir. Önceki inceleme raporlarının sunulması değerlendirme sürecini hızlandıracaktır. Kongre ve toplantılarda sunulan yazılarda yazının sunulduğu toplantının kongrenin adı, tarihi ve yeri de dahil olmak üzere ayrıntılı bilgi ile birlikte sunulmalıdır.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen yazılar çift kör hakemlik sürecinden geçecektir. Her bir yazı tarafsız bir değerlendirme süreci sağlamak için alanda uzman en az iki harici, bağımsız hakem tarafından incelenecektir. Baş editör, tüm başvurular için karar alma sürecindeki nihai otoritedir.

Yazarlardan deneysel, klinik ve ilaç çalışmaları ve bazı vaka raporları için gerekirse, etik kurul raporları veya eşdeğer bir resmi belge istenecektir. İnsanlar üzerinde yapılan deneysel araştırmalarla ilgili yazılar için, hasta ve gönüllülerin yazılı bilgilendirilmiş olurlarının alınabileceği prosedürlerin ayrıntılı bir açıklamasının ardından elde edildiğini gösteren bir ifade eklenmelidir. Hayvanlar üzerinde yapılan çalışmalarda, hayvanların acı ve ıstıraplarını önlemek için alınan önlemler açıkça belirtilmelidir. Hasta onamı, etik komite adı ve etik komite onay numarası hakkında bilgi de makalenin Materyal-Metod bölümünde belirtilmelidir. Hastaların anonimliklerini dikkatlice korumak yazarların sorumluluğundadır. Hastaların kimliğini ortaya çıkarabilecek fotoğraflar için, hasta veya yasal temsilcisi tarafından imzalanan bültenler eklenmelidir.

Tüm başvurular intihal araştırılması için yazılımsal olarak (iThenticate by CrossCheck) taranır.

İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu COPE yönergelerine uygun olarak hareket eder.

Yazar olarak listelenen her bireyin Uluslararası Tıp Dergisi Editörleri Komitesi (ICMJE - www.icmje.org) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. ICMJE yazarlığın aşağıdaki 4 kritere dayanmasını önerir:

1. Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması

2. Dergiye gönderilecek kopyanın hazırlanması veya bu kopyayının içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması

3. Yayınlanacak kopyanın son onayı.

4. Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir.

Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir.

Yazı gönderim aşamasında ilgili yazarların, yazarlık katkı formunun imzalı ve taranmış bir versiyonunu (https://dergipark.org.tr/en/pub/tchd adresinden indirilebilir) Türkiye Çocuk Hastalıkları Dergisi'ne göndermesini gerektirir. Yayın kurulu yazarlık şartarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir. Makalenin gönderilmesi aşamasında bir yazar makalenin gönderilmesi ve gözden geçirilmesi aşamalarında tüm sorumluluğu üstlenmeyi kabul ettiğini bildiren kısa bir açıklama göndermelidir.

Türkiye Çocuk Hastalıkları Dergisi'ne gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Yayın Kuruluna bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, ICMJE Potansiyel Çıkar Çatışması Bildirim Formu, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Yayın Kurulu tarafından COPE ve ICMJE yönergeleri kapsamında çözümlenecektir.

Derginin Yayın Kurulu, tüm itiraz durumlarını COPE kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir.

Yazarlar Türkiye Çocuk Hastalıkları Dergisi'ne bir yazı gönderirken, yazıların telif haklarını Türkiye Çocuk Hastalıkları Dergisi'ne devretmiş olmayı kabul ederler. Yayınlanmamak üzere reddedilirse veya herhangi bir sebepten yazı geri çekilirse telif hakkı yazarlara geri verilir. Türk Türkiye Çocuk Hastalıkları Dergisi'ne ait Telif Hakkı Devri ve Yazarlık Formları (https://dergipark.org.tr/tr/pub/tchd adresinden indirilebilir). Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayınlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir.

Yazıların sonuçlarının rapor edilemesi sırasında genellikle istatistiksel analizler gereklidir. İstatistiksel analizler uluslararası istatistik raporlama standartlarına uygun olarak yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Tıp dergilerine katkıda bulunanlar için istatistiksel yönergeler. Br Med J 1983: 7; 1489-93). İstatistiksel analizler hakkında bilgi, Materyal ve Metot bölümünde ayrı bir alt başlık ile açıklanmalı ve bu süreçte kullanılan istatistiksel yazılımlar mutlaka belirtilmelidir.

Türkiye Çocuk Hastalıkları Dergisi'nde yayınlanan yazılarda belitilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

YAZILARIN HAZIRLANMASI

Yazılar, Tıbbi Çalışmalarda Bilimsel Çalışmanın Yürütülmesi, Raporlanması, Düzenlenmesi ve Yayınlanması için Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (ICMJE)) Önerileri'ne uygun olarak hazırlanmalıdır (Aralık 2019'da güncellenmiştir - http://www.icmje.org/icmje-recommendations). Bu liste aşağıda görülebilir.

CONSORT	Randominize kontrollü çalışma
STROBE	Gözlemsel epidemiyolojik çalışmalar
STARD	Tanı yöntemleri
PRISMA	Sistemetik derleme ve metaanaliz
ARRIVE	Deneysel hayvan çalışmaları
TREND	Randomize olmayan tutum ve davranış çalışmaları

Yazılar yalnızca derginin çevrimiçi (online) makale gönderme ve değerlendirme sistemi aracılığıyla gönderilebilir.

www.dergipark.org.tr/en/journal/2846/submission/step/manuscript/new. Başka herhangi bir araç aracılığıyla gönderilen yazılar değerlendirmeye alınmayacaktır.

Dergiye gönderilen yazılar öncelikle sekreterlik tarafından yazının derginin kurallarına uygun olarak hazırlanıp hazırlanmadığı yönünden teknik bir değerlendirme sürecinden geçecektir.

Derginin yazım kurallarına uymayan yazılar, düzeltme talepleriyle birlikte gönderen yazara iade edilecektir.

Yazarların yazıları hazırlarken ve sisteme yüklerken aşağıdaki konulara dikkat etmesi gerekmektedir:

Telif Hakkı Devri ve Yazarlık Formunun Kabulü ve ICMJE tyarafından önerilen Potansiyel Çıkar Çatışması Bildirim Formu İlk başvuru sırasında (katkıda bulunan tüm yazarlar tarafından doldurulmalıdır) sisteme yüklenmelidir. Bu formları www.dergipark.org.tr/tr/pub/tchd adresinden indirebilirsiniz.

Kapak SayfasınınHazırlanması:

Kapak sayfası tüm yazılarla birlikte gönderilmeli ve bu sayfa şunları içermelidir:

Yazının kapak sayfasında yazının İngilizce başlığı bulunmalıdır. Kapak sayfası yazarların adlarını, akademik ünvanlarının, ORCID numaralarını, kurumsal/mesleki bağlantılarını, yazının kısa başlığını (en fazla 50 karakter), kısaltmaları, finansal açıklama bildirimini ve çıkar çatışması bildirimini içermelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse yazılar için Türkçe bir başlık da gereklidir. Bir yazı birden fazla kurumdan yazar içeriyorsa, her yazarın adını, ayrı olarak listelenen kurumlarına karşılık gelen bir üst simge numarası izlemelidir. Tüm yazarlar için için isim soy isim, e-posta adresi, telefon ve faks numaraları dahili iletişim bilgileri verilmelidir. Ayrıca yazı ile ilgili olrak iletişim kurulacak sorumlu sorumlu yazarın kim olduğu belirtilmelidir.

Önemli Uyarı: Kapak sayfası ayrı bir belge olarak yüklenmelidir.

Derleme türü makalelerde özet tek paragraf olacak şekilde hazırlanmalı e 300 kelime ile sınırlı olmalıdır. Bölümlendirilmiş özet hazırlanmasına gerek yoktur. Derlemeler 8000 kelime ve 60 kaynak ile sınırlandırılmaya çalışılmalıdır.

Anahtar kelimeler:

Özetin sonunda konu indeksleme için her gönderime en az üç en fazla altı anahtar kelime eklenmelidir. Anahtar kelimeler kısaltma olmadan tam olarak listelenmelidir. Anahtar kelimeler "National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html)" veritabanından seçilmelidir. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe anahtar kelimeler de gereklidir.

YAZI TÜRLERİ

Orijinal Araştırma Makalesi

Kelime sayısı: En çok 3500 kelime (Başlık, özet, anahtar kelimeler, kaynaklar, tablo ve figür yazıları hariç).

Ana metnin içereceği bölümler: Giriş, Yöntemler, Sonuçlar, Tartışma

Başlık: En çok 20 kelime

Yapısal özet: En çok 250 kelime. Bölümler: Amaç, Gereç ve Yöntem, Sonuçlar ve Tartışma

Anahtar kelimeler: En az 3 en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınırı yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Kaynaklar: En çok 40.

Orijinal makaleler; İngilizce başlık, İngilizce yapılandırılmış özet (yapılandırılmış, İngilizce anahtar kelimeler. Yazı Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe yapılandırılmış özet (Amaç, Gereç ve Yöntem, Sonuç ve Tartışma olarak yapılandırılmıştır) ve Türkçe anahtar kelimeler de gereklidir.

Çoğu okuyucu ilk olarak başlık ve özeti okuduğu için bu bölümler kritik öneme sahiptir. Ayrıca, çeşitli elektronik veritabanları yazıların sadece özetlerini indekslediklerı için özette önemli bulgular sunulmalıdır.

Makalenin diğer bölümleri Giriş, Gereç ve Yöntemler, Sonuçlar, Tartışma, Teşekkür (gerekirse) ve Kaynaklar'dan oluşmalıdır. Makalelerin tüm bölümleri yeni bir sayfada başlamalıdır.

Derleme:

Kelime sayısı: En fazla 5000

Özet: En fazla 500 kelime

Anahtar kelimeler: En az üç en fazla altı kelime, alfabetik olarak sıralanmıştır.

Şekiller ve tablolar: Sayı sınır yok ancak tam olarak gerekçelendirilmeli ve açıklayıcı olmalıdır.

Kaynaklar: 80'e kadar

Derleme makaleleri, tıptaki belirli konuların kapsamlı olarak gözden geçirildiği, konunun tarihsel gelişimini, mevcut bilinenleri, araştırıma ihtiyacı olan alanları içeren yazılarır. Konu hakkında orijinal araştırmaları yazarlar tarafından yazılmalıdır. Tüm derleme yazıları kabulden önce diğer yazılara eşdeğer değerlendirme süreçlerine tabi tutulacaktır.

Derleme makaleleri şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Derleme Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe özet ve Türkçe anahtar kelimeler de gerekmektedir.

Olgu Sunumu:

Kelime Sayısı: En fazla 2000 kelime

Özet: En fazla 200 kelime

Anahtar Kelime: En az üç en fazla altı kelime

Tablo ve Şekil: Toplamda en fazla beş ile sınırlandırılmıştır.

Kaynaklar: En fazla 15

Dergiye sınırlı sayıda olgu sunumu kabul edilmektedir. Olgu sunumlarının tanı ve tedavide zorluk oluşturan, nadir, literatürde yer almayan yeni tedaviler sunan ilginç ve eğitici olguların seçilmesine dikkat edilmektedir. Olgu sunumu giriş, olgu sunumu ve tartışma içermelidir.

Olgu sunumları şunları içermelidir; İngilizce başlık, İngilizce özet ve İngilizce anahtar kelimeler. Türkiye'de bulunan bir merkez tarafından gönderilmişse Türkçe başlık, Türkçe özet ve Türkçe anahtar kelimeler de gereklidir.

Editöre mektup:

Kelime sayısı: En fazla 1500 kelime

Şekil ve tablolar: En fazla 3

Kaynaklar: En fazla 15

Editöre mektup daha önce yayınlanmış bir makalenin önemli bölümlerini, gözden kaçan yönlerini veya eksik bölümlerini tartışır. Dergi kapsamında okurların dikkatini çekebilecek konularda, özellikle eğitici vakalarda yer alan yazılarda editöre mektup şeklinde de gönderilebilir. Okuyucular ayrıca yayınlanan yazılar hakkındaki yorumlarını editöre mektup şeklinde sunabilirler. Bir özet ve Anahtar Kelimeler dahil edilmemelidir. Tablo, şekil, görüntü içerebilir. Metin alt başlıkları içermemelidir. Yorum yapılan makaleye bu yazının içinde uygun şekilde atıfta bulunulmalıdır.

Editöre mektuplar; İngilizce başlık. Türkiye'de bulunan bir merkez tarafından gönderilmişse editör mektubu için Türkçe bir başlık da gerekmektedir.

Çalışma Metodları:

Türkiye Çocuk Hastalıkları Dergisi araştırmanın şeffaflığını artırmak ve devam etmekte olan araştırmalar hakkında ilgili kişileri bilgilendirmek için çalışma metodları yayınlamaktadır. Çalışma metodlarının yayın kararı editör tarafından verilmektedir. Pilot çalışmaların veya fizibilite çalışmalarının metodları genellikle yayınlanmamaktadır.

Çalışma metodları yazıları, çalışmanın hipotezi, gerekçesi ve metodolojisi hakkında ayrıntılı bir açıklama sunan SPIRIT yönergelerine uymalıdır. Tüm çalışmalar için etik kurul onayı alınmış olmalıdır. Klinik araştırmalar için tüm protokoller, araştırma kayıt numarasını ve kayıt tarihi verilmelidir.

Tablolar

Tablolar, referans listeden sonra ana belgeye dahil edilmelidir ana metin içine yarleştirilmemelidir. Ana metinde atıfta bulundukları sırayla numaralandırılmalıdır. Tabloların üzerine açıklayıcı bir başlık konulmalıdır. Tablolarda kullanılan kısaltmalar ana metinde tanımlansalar bile tabloların altında dipnotlarla tanımlanmalıdır. Tablolarda sunulan veriler, ana metinde sunulan verilerin tekrarı olmamalı, ancak ana metni desteklemelidir. Kısaltmalar için aşağıdaki semboller sırayla kullanılmalıdır: *, †, ‡, §, ||, ¶, **, †→, ‡‡.

Şekiller ve şekil alt yazıları

Şekiller, grafikler ve fotoğraflar, gönderim sistemi aracılığıyla ayrı dosyalar (TIFF veya JPEG formatında) olarak gönderilmelidir. Dosyalar bir Word belgesine veya ana metne yerleştirilmemlidir. Şekil alt birimleri olduğunda, alt birimler tek bir görüntü oluşturacak şekilde birleştirilmemeli, her alt birim, başvuru sistemi aracılığıyla ayrı ayrı yüklenmelidir. Resimlerin üzerine etiketleme (örneğin a,d,c,d gibi) yapılmamalıdır. Şekil altyazılarını desteklemek için görüntülerde kalın ve ince oklar, ok uçları, yıldızlar, yıldız işaretleri ve benzeri işaretler kullanılabilir. Görüntülerde bir bireyi veya kurumu gösterebilecek her türlü bilgi kör edilmelidir. Gönderilen her bir şeklin çözünürlüğü en az 300 DPI olmalıdır. Değerlendirme sürecinde gecikmeleri önlemek için, gönderilen tüm şekiller net ve büyük boyutlu olmalıdır (en küçük boyutlar: 100 × 100 mm). Şekil açıklamaları ana metnin sonunda metindeki sıraya göre ayrı ayrı listelenmelidir.

Makalede kullanılan tüm kısaltmalar ve akronimler, hem özet hem de ana metinde ilk kullanımda tanımlanmalıdır. Kısaltma, tanımın ardından parantez içinde verilmelidir.

Ana metinde bir ilaç, ürün, donanım veya yazılım programından bahsedildiğinde, ürünün adı, ürünün üreticisi ve şehri ve şirketin ülkesini (ABD'de ise eyalet dahil) içeren ürün bilgileri, parantez içinde aşağıdaki biçimde sağlanmalıdır: The skin prick tests were performed using a multi-prick test device (Quantitest, Panatrex Inc, Placentia, California, USA)

Tüm referanslar, tablolar ve şekiller ana metin içinde belirtilmeli ve ana metin içinde belirtildikleri sırayla numaralandırılmalıdır. Orijinal makalelerin kısıtlılıkları tartışma bölümü içinde sonuç paragrafından önce belirtilmelidir.

KAYNAKLAR

Yayınlara atıf yapılırken, en son ve en güncel yayınlar tercih edilmelidir. Yazarlar on yıldan eski referansları kullanmaktan kaçınmalıdır. Yazılarda 10 yıldan eski tarihli referans sayısının toplam referans sayısının %20'sini geçmemesine dikkat edilmelidir. Elektronik olarak yayınlanmış ancak cilt ve sayfa numarası verilmemiş yazılar atfedilirken DOI numarası verilmelidir. Yazarlar kaynakların doğruluğundan sorumludur. Referans numaraları metindeki cümlelerin sonunda metinde kullanıldıkları sıra ile numaralandırılmalıdır. Dergi adları "Index

Medicus" veya "ULAKBIM/Turkish Medical Index" de listelendiği gibi kısaltılmalıdır. Mümkün olduğunca yerel referanslar kullanılmalıdır. Kaynaklar aşağıdaki örneklere uygun olarak yazılmalıdır.

Kaynak dergi ise;

Yazar(lar)ın soyadı adının başharf(ler)i (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan makaleler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi) kullanılmalıdır. Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi

(http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt:İlk ve son sayfa

numarası.

Örnek: Benson M, Reinholdt J, Cardell LO. Allergen-reactive antibodies are found in nasal fluids from patients with birch polen-induced intermittent allergic rhinitis, but not in healthy controls. Allergy 2003;58:386-93.

Kaynak dergi eki ise;

Yazar(lar)ın soyadı adının başharf(ler)i. Makalenin başlığı. Derginin Index Medicus'a uygun

kısaltılmış ismi (http://www.ncbi.nlm.nih.gov/sites/entrez/query.fcgi?db=nlmcatalog) Yıl;Cilt

(Suppl. Ek sayısı):İlk sayfa numarası-Son sayfa numarası.

Örnek: Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994; (102 Suppl 1):275–82.

Kaynak kitap ise;

Yazar(lar)ın soyadı, adının başharf(ler)i. Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Basımevi, Basım Yılı.

Örnek: Ringsven MK, Bond N. Gerontology and leadership skills for nurses. 2nd ed. Albany, NY: Delmar Publishers, 1996.

Kaynak kitaptan bölüm ise;

Bölüm yazar(lar)ının soyadı adının başharf(ler)i. Bölüm başlığı. In: Editör(ler)in soyadı, adının başharf(ler)i (ed) veya (eds). Kitabın adı. Kaçıncı baskı olduğu. Basım yeri: Yayınevi,

Baskı yılı:Bölümün ilk ve son sayfa numarası.

Örnek: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM (eds). Hypertension: Pathophysiology, Diagnosis, and Management. 2nd ed. New York: Raven P, 1995:466–78.

Kaynak toplantıda sunulan bildiri ise;

Yazar(lar)ın soyadı adının başharf(ler)i. (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan bildiriler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi kullanılmalıdır).Bildirinin başlığı. Varsa In: Editör(ler)in soyadı adının başharf(ler)i (ed) veya (eds). Kitabın adı. Toplantının adı; Tarihi; Toplantının yapıldığı şehrin adı, Toplantının yapıldığı ülkenin adı. Yayınevi; Yıl. Sayfa numaraları.

Örnek: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O (eds). MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992. p. 1561-5.

Kaynak elektronik dergi ise;

Yazar(lar)ın soyadı adının başharf(ler)i. (6 ve daha az sayıda yazar için yazarların tümü, 6'nın üzerinde yazarı bulunan makaleler için ilk 6 yazar belirtilmeli, Türkçe kaynaklar için "ve ark.", yabancı kaynaklar için "et al." ibaresi kullanılmalıdır). Makalenin başlığı. Derginin Index Medicus'a uygun kısaltılmış ismi Yıl; Cilt (Sayı). Available from: URL adresi. Erişim tarihi: Gün.Ay.Yıl.

Örnek: Arrami M, Garner H. A tale of two citations. Nature 2008;451(7177): 397-9. Available from: URL:www.nature.com/nature/journal/v451/n7177/full/451397a.html. Aaccessed 20 January 2008.

Kaynak web sitesi ise:

Web sitesinin adı. Erişim tarihi. Available from: Web sitesinin adresi.

Örnek: Centers for Disease Control and Prevention (CDC). Erişim tarihi: 12 Mart 2013. Available from: http://www.cdc.gov/

Kaynak tez ise:

Yazarın soyadı adının baş harfi. Tezin başlığı (tez). Tezin yapıldığı şehir adı: Üniversite adı (üniversite ise); Yılı.

Örnek: Özdemir O. Fibrillin-1 gen polimorfizmi ve mitral kapak hastalığı riski. (Tez). Ankara: Gazi Üniversitesi, 2006."

Düzeltme istenmesi aşaması:

Bir makalenin hakemler tarafından istenen değişiklikler yapılmış kopyası gönderilirken yazar, hakemler tarafından istenen her açıklama/düzeltmeye cevap vermekle yükümlüdür. Yazarlar hakemlerin düzeltme/açıklama isteklerini her isteğin ardından olacak şekilde madde madde açıklmalı, düzeltilmiş kopyaya yazılacak metin bu açıklamanın altına eklemelidir. Düzeltme yapılmış kopya dergiye ayrı bir kopya olarak yüklenmelidir. Düzeltilmiş yazılar düzeltme isteğinin gönderilmesinden itibaren 30 gün içinde gönderilmelidir. Yazının düzeltilmiş kopyasıistenilen sürede gönderilmezse yazı sistemden ototmatik olarak düşürülecektir ve tekrar başvuru yapılması gerekecektir. Eğer yazarlar ek zaman talep ediyorlarsa bu taleplerini ilk 30 günlük süre sona ermeden önce dergiye iletmelidir.

Kabul edilen yazılar dilbilgisi ve noktalama işaretleri yönünden kontrol edilir. Kabul süreci ve düzenleme işlemleri tamamlandıktan sonra yazı dergi web sayfasında cilt ve sayfa numarası verilmeden DOI verilerek yayınlanır.

Yazar Listesi/Sırası Değişimi

Yazı gönderildikten sonra yazar listesinin/sırasının değiştirilmesi (yazar adlarının silinmesi veya yeni yazar adı eklenmesi gibi) talepleri yayın kurulunun onayına tabidir. Bu talep yazar değişiklik formunun doldurulup dergiye yüklenmesi ile talep edilebilir. Bu form aşağıdakileri içerecek şekilde doldurulmalıdır: Talebin gerekçesi, yani yazar listesi, tüm yazarlar tarafından (yeni ve eski) imzalanan yeni bir telif hakkı transfer formu, yeni yazar tarafından imzalanmış çıkar çatışması formu.

Yazının Geri Çekilmesi Talebi

Türkiye Çocuk Hastalıkları Dergisi yüksek kaliteli yazılar yayınlamayı ve yayın etiğini korumayı taahhüt etmektedir. Yazarlardan, yayın etiğinde ve yazıların kalitesinde tavsiye edilen kurallara uymaları beklenmektedir.

Yazının geri çekilme talebi olağanüstü durumlarda talep edilmelidir. Bir yazının geri çekilmesi için yazarların dergiye geri çekme nedenlerini belirten ve tüm yazarlar tarafından imzalanan bir "Makale geri çekme Formu" yüklemeleri gerekmektedir. Bu form derginin web sayfasından indirilebilir. Yazarlar dergiden bu konuda olumlu bir cevap alana kadar makalelerinin geri çekilme işleminin tamamlanmadığını bilmelidir.

Bir makalenin inceleme süreci altı aydan uzun bir zaman almış ve yazarlara karar bildirilmemişse yazının geri çekilme talebi olumlu karşılanır.

INSTRUCTIONS FOR AUTHORS

The Turkish Journal of Pediatric Disease is an open access and a scientific publication journal that is published from the Ankara City Hospital, Children's Hospital. The journal is published in accordance with independent, unbiased, and double-blind peer review principles. The journal is published bimonthly (January, March, May, July, September, November)

The publication language of Turkish Journal of Pediatric Disease is English. However, the journal welcomes manuscripts both in Turkish and English for the evaluation. The authors of articles who had manuscript in Turkish are required to provide an English version of their accepted article before the publication.

In the Turkish Journal of Pediatric Disease original articles, reviews, case reports, editorials, short reports, book reviews, biographies and letters to the editor are also published in the journal. Besides if related with pediatrics, articles on aspects of pedatric surgery, dentistry, public health, genetics, pshyciatrics and nursery could be published.

The editorial and the publication processes of the journal are shaped in accordance with the guidelines of the World Association of Medical Editors (WAME), the Committee on Publication Ethics (COPE), the International Council of Medical Journal Editors (ICMJE), the Council of Science Editors (CSE), the European Association of Science Editors (EASE) and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The originality, high scientific quality, and the citation potential are the most important criterias for a manuscript to be accepted for the publication. Manuscripts submitted for the evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed if manuscript have been submitted to another journal for the evaluation and have been rejected for the publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with a detailed information of the organization, including the name, date, and location of the organization.

Manuscripts submitted to the Turkish Journal of Pediatric Disease will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field, in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of the research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for the experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts that are concerning experimental researchs on humans, a statement should be informed included that shows a written informed consent of the patients and the volunteers who were given a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information of the patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity carefully. For the photographs that may reveal the identities of the patients, releases signed by the patient or their legal representative should be enclosed.

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Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship should be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable of all aspects of the work in

ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she had done, an author should be able to identify which co-authors are responsible for the specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all of the four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all of the four criteria should be acknowledged in the title page of the manuscript.

The Turkish Journal of Pediatric Disease requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through https://dergipark.org.tr/en/pub/tchd) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without a further review. As a part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all of the responsibility for the authorship during the submission and review stages of the manuscript.

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Example: Centers for Disease Control and Prevention (CDC). Acsess date: 12 March 2013. Available from: http://www.cdc.gov/

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Derlemeler / *Reviews*

COVID-19 and Children: From an Epidemiological Perspective

COVID-19 ve Çocukların Etkilenimi: Epidemiyolojik Açıdan Değerlendirmeler

Banu CAKIR

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ABSTRACT

COVID-19, caused by SARS-CoV-2, has rapidly progressed globally started from early days of 2020 and was disseminated to 187 countries and territories by April. As of May 3, 2020, COVID-19 has led to a total of 3,507,442 cases and 245,241 related deaths, globally. Turkey, was successful to delay the first COVID-19 case until March 10, yet, case numbers increased fast, reaching to the top 7th rank in the list of countries with the highest case numbers. It is fortunate that the case-fatality ratio was relatively low, with a somewhat stable course around 2.5%. Somewhat stable course of new case numbers, with an apparent decrease through the end of April led to onset of normalization attempts in the country. The future course of the pandemic will be mainly determined by compliance of the general public with personal hygiene, mask use and social distancing.

Globally, COVID-19-related morbidity and mortality rates are lower among children than in adults. Underlying mechanisms for this difference has not been clarified, yet, may be linked to lower exposure rates among children, their immune response may be different and/or higher rates of asymptomatic cases may have lower admissions/testing among children. However, it is important to emphasize that children are prone to SARS-CoV-2, too and all relevant preventions should be ensured. This issue should also be considered in evaluating potential risk of infection transfer from asymptomatic youngsters to the elderly and/or to those with chronic diseases.

Data on COVID-19-related case numbers and deaths in Turkey have not been published so far for children. This requires urgent consideration for related reporting and novel research activities on health burden of COVID-19 on Turkish children. Success in combating the COVID-19 pandemic requires concurrent efforts for clinical management of patients together with epidemiological studies of available national data and establishment of specific research to provide evidence for national and international preventive interventions. Learnings from this pandemic will provide direct evidence for management of future pandemics, and all related parties should be motivated to prepare detailed reporting of ongoing efforts and their outputs.

Key Words: COVID-19, Child health, Epidemiology, Transmission, Prevention

ÖZ

SARS-CoV-2 virüsünün neden olduğu COVID-19 hastalığı, 2020 yılının ilk günlerinden itibaren hızla yayılarak, Nisan ayı sonunda 187 ülke ve bölgeye yayılım göstermiş; 3 Mayıs 2020 itibarı ile dünyada 3,507,442 vaka ve ilişkili 245,241 ölüme neden olmuştur. Türkiye, ilk vakanın görüldüğü 10 Mart 2020 tarihinden sonra vaka sayılarındaki hızla artma sonucu 50 gün içinde vaka sayısı en yüksek 7. ülke konumuna yükselmiş, ancak bu arada ölüm sayılarını göreceli olarak aşağı sınırlarda (%2.5 civarında) tutmayı başarmıştır. Nisan ayının sonuna doğru vaka sayılarında düzleşme ve aşağı doğru gidiş ile gündelik yaşamdaki kısıtlamaların azaltılması konusundaki çalışmalar başlamıştır. Toplumun kişisel hijyen, sosyal mesafenin korunması ve maske kullanımına uyum düzeyine bağlı olarak salgının ülkemizdeki süreci değişiklik gösterebilecektir.

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Dünya genelinde çocukluk çağında COVID-19 vaka ve ölüm sayıları, yetişkinlere kıyasla daha düşüktür. Bunun altında yatan nedenler çocukların enfeksiyonla daha az karşılaşmaları, bağışıklık sistemi cevaplarının yetişkinlerden farklı olması ve/veya asemptomatik olmaları nedeniyle daha az hastane başvuru/test yapılması kaynaklı olabileceği konusunda yayınlar olsa da sonuçları henüz kesinlik kazanmamıştır. Öte yandan, COVID-19 pandemisinin çocukların yaşamı için de bir risk olduğu kesindir ve bu konuda yeterli önlemler alınmalıdır. Bu paralelde asemptomatik ve sağlıklı görünümdeki çocukların enfeksiyonu taşıma konusundaki tehlike hem topluma yönelik kısıtlamalar planlanırken hem de özellikle yaşlı ve kronik hastalığı olan kişilerin bireysel korunmasında dikkate alınmalıdır.

Türkiye'deki vaka sayıları içinde çocuklara ait yüzdeler ve ilişkili risk faktörleri konusunda yayınlanmış bir bilgi henüz yoktur. Bu konuda yapılacak çalışmalara ivedikle ihtiyaç duyulmaktadır. Pandemi dahilinde bir yandan salgına bağlı hastalık yükü ile başa çıkarken, bir yandan da verilerin detaylı inceleme ve analizlerinin yapılması, literatüre katkı sağlayacak çalışmalar ile ulusal ve uluslararası mücadele planlarına katkı sağlanması değerlidir; bu pandemide öğrenilenlerin detaylı olarak yapılması bundan sonraki pandemiler için kanıta dayalı hazırlık sürecine doğrudan katkı sağlayacaktır ve desteklenmelidir.

Anahtar Kelimeler: COVID-19, Çocuk sağlığı, Epidemiyoloji, Bulaş, Korunma

INTRODUCTION

New Coronavirus Disease (COVID-19), caused by SARS-CoV-2 has evolved rapidly after the first case in January 2020, and has spread to 187 countries and territories globally by the end of April. Globally, a total of 3 507 442 COVID-19 cases and 245

241 related deaths were present on May 3, 2020 (1,2). This new disease was first noticed in Wuhan, China, late in December 2019, following detection of pneumonia clusters of undetected etiology; China reported this new disease to the World Health Organization (WHO) Country Office in China on December 31, 2019. The causative virus was first named as 2019-nCoV and the disease was named as the new coronavirus disease. Later, the nomenclature was revised as SARS-CoV-2 to relate its association with a Severe Acute Respiratory Syndrome and the disease was named as Coronavirus Disease, i.e., COVID-19 (3). WHO announced January 30 COVID-19 as a Public Health Emergency at International level due to rapid increase of case numbers across the World, including different continents, and its human-to-human transmission was clarified. WHO announced COVID-19 as a pandemic on March 11, 2020, when the disease was already present in 114 countries, leading to 18 000 cases and 4921 related deaths (4,5).

Pandemic is a communicable disease distributed to several countries in different continents. An announced pandemic requires several precautions for its spread, all of which could lead to restrictions in international relations, trade, educational activities, human movements including travels, etc. These could explain why WHO hesitated to announce COVID-19 as a pandemic, earlier. COVID-19 is an animal-related disease, similar to Influenza pandemics experienced in the World before. The most recent influenza H1N1 pandemic in 2009 was quite different than seasonal influenza outbreaks, occurring more common in young people, with enormous number of cases and fatality. Pandemic İnfluenza A (H1N1) virus is a mixed version of influenza viruses observed in humans, birds and pigs. It was first observed in Mexico in March 2009 and was further spread to several countries, alarmed by WHO as a pandemic disease on June 11, 2009. The disease started in the southern hemisphere first, and spread to the northern hemisphere by the beginning of winter (6).

Globalization, increased number of international travel and commerce, urbanization, crowded cities, shanty settlements, crowded households, increasing population of migrants, seasonal workers, homeless individuals and victims of political crisis have lead over the years to increase in the proportion of population that is prone to social inequalities, immunity problems, hunger etc., together with the increase in close contact of human beings with animals. All these have paved the way to a novel virus-related pandemic, yet, our recent experienced with COVID-19 revealed that the World was not ready to face a pandemic of such a huge size. Given that nobody is immune to this novel virus, it is not possible to stop transmission of this infection until an effective vaccine is invented and becomes highly available for all. (2). Emergence of this novel virus was first linked to some conspiracy theories; yet, laboratory work has clarified that SARS-CoV-2 is linked with a bat coronavirus. (7). Studies are ongoing to establish the underlying mechanisms and the intermediate host(s) for this new virus, but the scientists have already accepted SARS-CoV-2 as a "natural" virus and claim that similar novel viruses may appear in future years, as well. At this stage, it is essential to study SARS-CoV-2 and COVID-19 in depth, including predictors of infection and related fatality, and to work on developing effective medication(s) and vaccine(s) to eliminate this disease in the shortest period (8,9).

Globally, several institutions and hundreds of scientists have been working on vaccine development, and a few have already passed the first stages of testing in animals. Current treatment modalities include off-label use of several drugs, whilst new drug search is ongoing in several countries (19). Before an effective vaccine or medication is in hand, case numbers are expected to increase till the herd immunity threshold is reached. The threshold will depend on the basic reproductive number (R0) and the effective reproductive number (Re). Herd immunity threshold is expected to be at least 40%; which corresponds to a total case number of 32 million for Turkey, including at least 320 000 deaths (11). This is an unacceptably high toll and, thus,

all countries are trying to mitigate or suppress the pandemic as long as they can.

Similar to that in other pandemics, several population measures were undertaken in all populations, based on evidence in some, or simply as indicated by the health authority in others. In contrary to biomedical ethics, public ethics principles prioritize population's needs and social equity, which may sometimes restrict individual rights (such as, sheltering-in or quarantine measures). As allowed in disaster plans and by legislations, individuals and populations may be obliged to obey some restrictions in routine daily lives. In this context, several public restrictions were introduced to communities, starting early in the pandemic. This included travel restrictions in/out of some cities, closure of schools and public places, obligatory home-stays for those aged 20 years or below and for elderly. Mask use has become obligatory in public places including public transport, as pandemic evolves and normalization is initiated.

Mitigation plans aim stabilizing and decreasing new case numbers, providing some relaxation in social life, but risk groups (such as, elderly and those with chronic diseases) need to be protected to the maximum. Economical, social, mental and occupational consequences of total/partial restrictions need to be balanced with the number of actively infected individuals in the population; it is hard to balance the needs for population health versus losses in other areas of life. So far, Turkey has been trying mitigation methods based on provision of 100% compliance with personal hygiene, social distancing and mask use, with addition of stronger public restrictions, as needed.

In the pandemic, imposing public protective measures for children require a tedious plan to cover short term health effects of COVID-19, with its secondary effects on social life, family relations, educational needs, physical exercise, socialization etc., all of which will ultimately adversely affect their well-being.

Effects of COVID-19 Pandemic on Children's Health

Indicators of health in communicable diseases include incidence rate, attack rate, mortality and fatality rates. Real-time evaluations of health during a pandemic, measures such as new/cumulative case numbers, proportion of asymptomatic cases, descriptive characteristics of cases versus non-cases, the proportion of children among all cases and related deaths are easy to calculate, yet useful (12).

The COVID-19 pandemic initiated an unprecedented collaboration among scientists globally, and scientific publications are evolving rapidly to share experiences and learnings among scientists. LitCovid, a curated, web-based network under PubMed, gathers COVID-19-related publications in one site, enabling scientist to access full text manuscripts, even before completion of peer-reviews (13). In LitCovid, there were 10 528 medical papers published and cited in PubMed; of these, only 18 had a Turkish author as of May. Of all publications, 322 papers included the terms of "child" or "children" in the text. This review is based on literature obtained from LitCovid, and the recent review entitled "Coronavirus disease 2019 (COVID-19): Considerations in children" in UpToDate. Literature on COVID-19 in children is relatively scarce and manuscripts are mainly case reports, case series and descriptive work in type; more work on pathogenesis and treatment is anticipated as the pandemic evolves.

First cases in China led clinicians to consider COVID-19 as a disease of mainly elderly and those with comorbidities, with respiratory symptoms and relatively low fatality. Unfortunately, children were found to be at risk, as well, and can transmit disease to others, even when they are asymptomatic (14). Recent publications revealed that children at any age can get infected and develop disease (15-20). In the study of the Chinese Center for Disease Control and Prevention, based on data from 72.314 confirmed COVID-19 cases, only 1% was younger than 10 years old. Wuhan Children's Hospital in China is the only hospital in Wuhan for children under 16 years. COVID-19 test results in this hospital during the period from January 28 through February 26 revealed test-positivity in 12.3% of all children admitted to the hospital (16). The systematic review of all manuscripts published between January 1 and March 18, 2020, proportion of children in all cases ranged from 1% through 5% (21). In China, infection rate of children is 4%-7% in households where there is at least one COVID-19 case; transmission from children to adults in the household is not high, yet, almost all infections among children are through household contacts with adults. In South Korea, 7.1% of all confirmed COVID-19 cases before April 30, 2020 were aged 19 years or lower (18,22-23). Frequency of COVID-19 varies largely across geographic locations due to variations in exposure rates, effective contact numbers, case definitions, testing criteria and identification rate of (all) cases by the health system in a given location. Despite this finding, it is remarkable that proportion of children among confirmed cases are more or less similar in China, South Korea, Italy and USA. Centers for Disease Control and Prevention in USA (CDC), reported a total of 149 760 COVID-19 cases as of April 2, 2020: Of these, 1.7% were aged 18 years or below, and the majority were those residing in New York and New Jersey (18). Only 10% of the infected children provide a travel history prior to infection and all others are likely to be infected from household members or general population. The mean age of infected children is 11 years (0-17), and 53% of all are males 18,20). In China, the majority of infected children are again males (%57-%60), but the mean age [7 years (1-18)] is younger than that in USA population (14-15,17).

The proportion of youngsters among all COVID-19 cases is not sufficient per se to define the risk of COVID-19 in this population. Variations in definition of childhood in different populations, proportion of children in total population, accessibility to health services, testing criteria, availability of testing may cause bias in direct comparisons of COVID-19 case numbers among youngsters across different populations.

It is more appropriate to calculate age-specific and gender-specific, residence-specific (if possible) incidence rates for international comparisons. Current literature and several web-based COVID-19 dashboards provide 14-day cumulative case numbers, together with case numbers for 100 000 population to make comparisons more reliable (24). In comparisons, the onset of the pandemic in a given country is considered as t=0 for the date of the first notified COVID-19 case and comparisons are established at selected dates following day 0, with cumulative numbers presented out of 100.000/1.000.000 of population in that country. Even within a given country, such as in Turkey, availability and numbers of testing, testing criteria, accessibility and timing of testing may lead to underestimation of the numerator in incidence calculations, thus underestimate the true incidence rate in the population. Thus, all nations should provide information on testing criteria, case definition, validity and reliability of the tests used in reporting their COVID-19-related morbidity rates. Whenever follow-up is possible for selected populations (e.g., health workers, imprisoned individuals or nursing home residents), cumulative incidence rates can be calculated or prevalence-type case-control studies may also enable rate calculations for selected closed populations (25).

Age-specific incidence rates are valuable in defining proneness of children to COVID-19. In USA, distribution of confirmed COVID-19 cases by age groups are 11% among 1-4 years; 15% among 5-9 years; 27% among 10-14 years and 32% among those aged 15-17 years (20). European Surveillance System (TESSy) data of the European Center for Disease Control (ECDC), revealed that of all confirmed COVID-19 cases of 266 393 individuals, proportion of those under 10 years old was 1.1% and that only 2.5% was in 10-19 years old group. Under 18 years old, the male-to-female ratio of COVID-19 cases was about 1 (26).

Studies on age-specific incidence rates and related factors are clearly warranted to clarify whether children are less likely to be exposed to COVID-19 or whether they experience more asymptomatic or less severe disease when they get infected, compared to their adult counterparts. Besides direct effects of COVID-19 on child health, secondary effects through socioeconomic losses are likely to have adverse effects on underprivileged children's lives. (27). Future studies need to investigate such secondary effects upon completion of the pandemic. Intolerance to uncertainty, restrictions to daily routines, being away from school and friends, scare of death or family loss may lead to problems in nutrition and sleep disturbances among children. Long-term quarantines and long-term stay-home obligations may decrease physical exercise and increase addiction to television and computer, as well. Social and mental well-being needs to be supported during this time. Upon completion of the pandemic, children may again need support for returning back to their daily responsibilities and social relations.

Severity of COVID-19 among children

At first glance, COVID-19 pandemic was considered as a disease of adults mainly, and children were considered as being less prone to disease, with a 1-2 weeks of recovery period for those with disease. However, even fatal cases have been observed in children, later in the course of the pandemic (21, 28-34). Severity of infection is the most prominent under 1-year-old children but the underlying reasons are yet to be clarified (21). Comorbidity, e.g., chronic pulmonary disease (including, moderate-to-severe asthma), cardiovascular diseases, immunosuppression have been revealed as a predictor of disease severity among children with COVID-19, yet, this proportion is 23% of all cases (21). Hospitalization is needed for 6%-20% of children with COVID-19, with an indication for intensive care unit (ICU) care in 0.58%-2.00% among children hospitalized in USA hospitals. Similarly, in a study from China, 3 out of 19 children needed ICU care and ventilation; all 3 had comorbidity (18). In a study from Italy, of 1591 children, only 1% needed ICU care. A study of PICU-USA, a total of 106 children were given ICU care over the first 4 months of the pandemic, and only one of these children was lost (35). Scarcity of studies on COVID-19 in children, together with small sample sizes of available studies hinder our ability to command on natural course of COVID-19 among children, and disease severity-related risk factors are not clarified. Cohort studies are clearly warranted for conclusive results.

Several hypotheses on lower severity of COVID-19 among children compared to adult patients have been linked with immune response. In SARS and MERS, the main predictor of disease severity was linked to high viral load. The antibodies formed against the other coronavirus infections in childhood (NL63, 229E, OC43, HKU1) may lead to a decrease in severity of COVID-19 due to cross-reaction. Alternatively, quality and quantity of viral receptors in children may be different than those in adults. The S protein in the viral protein structure determines CoV-2 entrance into the cell. The RBP domain of S1 is involved in receptor binding, thus, dominates the proneness of tissues to Corona viruses. SARS-CoV-2 has been shown to enter human cells via angiotensin-converting enzyme 2 (ACE2) receptors. The high affinity of SAR-CoV-2 to ACE-2, makes organs with high ACE-2 receptors (including kidneys, small intestine, testis and lungs) at risk for damage. If ACE-2 protein formation, distribution and number are different across age groups, the intracellular response to alveolar epithelial cell damage will be less in children, compared to that in adults. Low prevalence of comorbidity in childhood may also explain the lower severity of COVID-19 infection among children. All these hypotheses regarding severity of COVID-19 in children warrant further research for conclusive results (36-39). Of the

728 lab-confirmed COVID-19 cases in children in China, about 55%-60% of the cases had mild-to-moderate disease severity (8). The most severe cases in children are reported in infancy, with a prevalence of severe disease in 1/10th of all COVID-19 cases. Caution is needed in interpretation of studies in children, given the limited quality of data collected during active pandemic period, non-standardized nature of testing and/or treatment modalities, variations in accession rate and time to hospitalization and absence of testing in urgent situations for handling severe diseases. Also, presence of any concurrent viral respiratory infections should be identified. Longitudinal case-series and cohort studies are necessary to answer such situations.

Signs and symptoms of COVID-19 in children

Signs and symptoms of COVID-19 are similar in children to that in adults but are less prominent (8), and the course of disease is milder among children (20). The most common symptoms of COVID-19 are fever and cough, followed by difficulty in breathing (18). Among 291 COVID-19 cases in USA, at least one of these symptoms appeared in 3 out of 4 children with the disease (18-20). COVID-19 may be observed in infancy without any symptoms, but fever. Of the 1491 children hospitalized for COVID-19 in Wuhan Children Hospital, the most common symptoms were cough (49%), fever (42%) and pharyngeal erythema (46%). Less commonly reported symptoms included nasal congestion, rhinorrhea, diarrhea, fatigue and vomiting. Among hospitalized patients, the majority had pneumonia (65%) and upper respiratory tract infection (19%). Remarkably, some children admitted by gastrointestinal symptoms, only (18). Rare symptoms included chills, myalgia, headache and loss of smell or appetite (40,41). Recently, some children with COVID-19 reportedly admitted to hospitals with symptoms resembling toxic shock syndrome and atypical Kawasaki syndrome (abdominal pain, gastrointestinal symptom, myocarditis, etc.). These children had high levels of CRP, erythrocyte sedimentation rate and ferritin (42, 43). In New York, a girl admitting to hospital with fever and rash was later tested positive for COVID-19, and a case-report was published to describe this case. Similar cases appeared also in the United Kingdom, Italy and Spain; all these were reported as hyper immune reactions due to prior infections. Between April 17 and May 1, only in New York hospitals, 15 children aged between 2 and 15 years old were treated with Kawasaki-like syndromes: four of these were COVID-19 test-positive, whilst the other 6 had antibodies against SARS-CoV-2. All children recovered, only one needed , a “hot topic bias” and “increased alertness/ familiarity of physicians” might have led this finding, as well. A severe case with Kawasaki-like syndrome and PCR-positivity for SARS-CoV-2 died in New York, recently. Altogether, this issues needs to be studied further.

Besides milder symptoms of COVID-19 among children, PCR test positivity rates are also lower than that in adults. Among symptomatic children PCR-positivity was 12% and only 16% of children with PCR-positivity had any symptoms (9). These may make infected children act as “super-spreaders” for the elderly in household setting or in close vicinity (45). A thorough clinical examination and testing are necessary for children with contact history and/or symptom; testing should be repeated, if needed; and, schooling should be discussed cautiously in those with contact history, regardless of symptoms. In estimation of herd immunity, the number of children with passed COVID-19, yet, remained undetected should be investigated. Also, the association between symptomatic status and epidemiologic and virological findings deserves to be well studied for clarification of pathogenesis in children.

In Wuhan, of all children with confirmed COVID-19 diagnoses, one-fourth had leucocyte count less than 5.5 x 109/L, in 3.5%, lymphocyte count was below 1.2 x 109/L (8); procalcitonin was high (>46 pg/mL) in 64% and one in every five children C-reactive protein was also high (>10 mg/L). Chest X-rays varied greatly, from no changes to bilateral consolidation (46,47). Of 171 children with confirmed COVID-19, 33% had ground-glass appearance in thoracic CTs, 19% had patchy spots and 12% had bilateral opacities (16,35). Some studies revealed that the majority of radiological changes appeared prior to symptoms (48,49). In 8 children with COVID-19, lung ultrasonography revealed sub-pleural consolidation and B lines (50).

In vitro transmission and risk of breast-feeding

COVID-19 appeared in a variety of different forms in pregnant women, ranging from asymptomatic or mild case status to leukocytosis and consolidation in thoracic tomographies. Two pregnant women with COVID-19 were treated in ICU, yet, the details of their disease status are not known. Scarcity of the number of studies on COVID-19 in pregnant women points at a need for future case-series and/or cohorts for conclusive results (35,51).

Similarly, literature knowledge on possibility of intra-uterine or prenatal transmission is scarce. Some recommends cesarean section when COVID-19 is present in pregnant woman. Yet, vaginal delivery has not been shown to lead to any COVID-19 transmission to the new born, to date. In 30 newborns of COVID-19 mothers have recently been shown to have no virus, yet, a few had perinatal complications and SARS-CoV-2 positivity in their placentae (35).

Transmission of SARS-CoV-2 through breast-feeding has not been studied adequately. Of the 6 breastfeeding mothers with COVID-19, no virus was detected in breast milk, however, close contact of mom and the baby and infected droplets may lead to transmission to the newborn, thus, individual protective measures are needed (52).

COVID-19 and Children: Experience in Turkey

The first COVID-19 case in Turkey was reported on March 11, 2020; seven days later, the first COVID-19 case with a domestic contact was announced by the Ministry of Health (MoH), together with the first COVID-19-related death. Since then, daily media announcements of the MoH have been providing data on numbers of new cases and deaths, those in ICU and patients requiring mechanical ventilation, together with daily test numbers (53). As of May 4, 2020, a total of 1 171 138 PCR test were done; a total of 127 659 cases and 3 461 were detected. Unfortunately, age-specific distributions are unknown.

The national burden of COVID-19 and related death toll need to be investigated further for their associations with related risk factors for providing robust evidence for public preventive measures. In this sense, we need more detailed analysis of national data providing specific distributions of cases by age, gender, residential setting, history of contact, date of diagnosis, and comorbidity. It is important to investigate distributions by date of infection, date of hospitalization, and clinical characteristics for those admitted to hospital. Epidemiologic studies on proportion of children among all cases, percent of those with symptoms and transmission rates among children will be valuable. Effectiveness of treatment modalities and types and frequencies of adverse effects (if any) need to be investigated. All such data will be useful for policy makers to base their decisions on robust evidence and to forecast the future of the pandemic under different scenarios.

In Turkey, following the rapid increase in case numbers, various combinations of public and individual measures enabled a steady state for some time, and daily death numbers decreased to below than 100. This control in numbers was perceived by the majority of population that the *"peak value is reached and the numbers will go down soon*". However, high transmission rates and human-to-human transmission make COVID-19 a hard pandemic to control, unless an effective vaccine is found and becomes available for everyone. Given that nobody is immune to this novel virus, a herd immunity (of about 40%-60% infection for an average R0 value of 2.5-3) means thousands of deaths, which is not acceptable for any country. So far almost 40 000 mutations are reported in SARS-CoV-2, yet, none has led to any significant change in clinical picture. So far, seasonal effects have not affected the course of pandemic, either. Altogether, countries need to comply with strict individual measures (masking, social distancing and hygiene), and public measures tailored to local needs may sometimes need to be strengthened to decrease cases under affordable numbers for the health care system.

Turkey has been successful so far to mitigate the pandemic without causing a shut down in the health system, yet, it is important to consider COVDI-19 as a long-term health problem and all sectors need to excogitate "effective survival methods" in the presence of the pandemic. In the meanwhile, scientists will continue to work on effective medications and vaccine(s), based on evolving literature on pathogenesis of COVID-19 in adults and children. Public messages need to be informative, transparent and uniform . It is important to convey the messages based on concrete evidence, not to evoke a false sense of safety or an unjustified panic in the population. It is important to collect objective, quantitative and comparable data; to provide timely and detailed reporting of available data for policy makers, and to share the novel information with colleagues across the nations. Pandemics cannot be avoided, yet, we can learn from them and use this knowledge to be ready for the upcoming ones.

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Treatment of children with COVID-19

Çocuklarda COVID-19 Tedavisi

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ABSTRACT

Currently, there is not any specific effective treatment for COVID-19. There are many studies published and ongoing especially on adult patients. Treatment options in pediatric patients are determined according to the agents used in adult patients. Although coronavirus disease 2019 (COVID-19) is mild in nearly all children, a small proportion of pediatric patients develop severe or critical illness. Supportive therapy forms the basis of the treatment as the symptoms and disease course in children are mild. There are currently no randomized controlled trials of drugs that can be used to treat COVID-19 in children. However, in severe clinical cases, the drugs used in adults are evaluated and used on a case-by-case basis. There is a growing need for well-designed controlled clinical trials to better define the safety and efficacy of potential treatments for COVID-19 in children.

Key Words: Children, COVID-19, Treatment

ÖZ

COVID-19 için halen spesifik etkili bir tedavi yoktur. Özellikle yetişkin hastalarda yayınlanmış ve devam etmekte olan birçok çalışma bulunmaktadır. Pediatrik hastalarda tedavi seçenekleri yetişkin hastalarda kullanılan ajanlara göre belirlenmektedir. Coronavirüs hastalığı 2019 (COVID-19) neredeyse çoğu çocukta hafif olarak geçirilmesine rağmen, hastaların küçük bir kısmında ciddi veya kritik hastalık gelişebilmektedir. Çocuklarda semptomlar ve hastalık seyri hafif olduğundan destekleyici tedavi tedavinin temelini oluşturur. Çocuklarda COVID-19'u tedavi etmek için kullanılabilecek, randomize kontrollü çalışması olan herhangi bir ilaç bulunmamaktadır. Bununla birlikte, kliniği ağır olan vakalarda, yetişkinlerde kullanılan ilaçlar vaka bazında değerlendirilirmekte ve kullanılabilmektedir. Çocuklarda COVID-19 için potansiyel tedavilerin güvenliğini ve etkinliğini daha iyi tanımlamak için iyi tasarlanmış kontrollü klinik çalışmalara artan bir ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Çocuk, Tedavi

INTRODUCTION

Currently, there is not any specific effective treatment for COVID-19. There are many studies published and ongoing especially on adult patients. Treatment options in pediatric patients are determined according to the agents used in adult patients. The majority of children with COVID-19 have a relatively mild and self-limited disease, and critical illness and mortality are rare. Therefore, isolation and supportive treatment of the patient have an important place. Other drugs in use for children with COVID-19 are also described in the following sections for severe cases.

1. Isolation of patients

Isolation of confirmed or suspected cases with asymptomatic and mild disease (these children have no respiratory difficulty, are feeding well, have SpO2 > 92%) at home or outpatient settings

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is recommended. Danger signs should be explained. House should be frequently ventilated. The patient should be asked to wear a simple surgical mask and asked to pay attention to cough hygiene. Hand hygiene should be provided in contact with the patient or their immediate environment. For patients isolated in the home, isolation is terminated after negativity is observed in 2 PCR samples taken at 24-hour intervals. Where testing is not possible, isolation is recommended for additional 14 days after symptoms resolved. For additional information for home care in COVID-19, please look at the website at reference (1).

2. Symptomatic and supportive care

There are minimal data about concerning using non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19 patients (2). Acetaminophen is preferred for antipyretic agent. Respiratory support, including supplemental oxygen and ventilatory support (noninvasive or invasive) should provide. Fluid and electrolyte balance should be regulated. Empiric antibiotics can use as indicated for community-acquired or health care-associated pneumonia; continuation of empiric antibiotics should be determined by cultures and other microbial tests and clinical condition. Bacterial coinfections appear to be infrequent in COVID-19 patients (3). Inhaled medications should be administered by metered dose inhaler, whenever possible, rather than through a nebulizer, to avoid the risk of aerosolization of SARS-CoV-2 through nebulization (4).

3. Antiviral agents

a. Hydroxychloroquine/chloroquine

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are aminoquinoline drugs used in the treatment and protection of malaria for more than 50 years and used in the treatment of inflammatory diseases including SLE and rheumatoid arthritis. Both drugs have a weak diprotic base feature and increase the pH in the endosomes, thereby suppressing the entry of the virus into the cell (5, 6). Hydroxychloroquine is an analogue of chloroquine and has fewer side effects than chlorocine (7). Many clinical trials investigating the safety and efficacy of chloroquine and hydroxychloroquine in COVID-19 pneumonia have been launched simultaneously in more than 10 hospitals in different states of China, including Wuhan. Considering the data that more than one hundred patients were examined, it was seen that the chloroquine phosphate group was better in relieving pneumonia exacerbation from the control group, improving radiological findings, cleaning the virus and shortening the disease duration. No chloroquine phosphate-related side effects have been reported in these patients. Following this, Chinese State officials agreed on the potent effect of chloroquine phosphate on COVID 19 pneumonia at the conference held on February 15, 2020, where decision-makers and regulators and executives of clinical studies took place, and entered the guideline recommendations of the Chinese Public Health Agency (8).

Both chloroquine and hydroxychloroquine have been reported to inhibit SARS-CoV-2 in vitro, although hydroxychloroquine appears to have more potent antiviral activity (9) . Randomized trials for their clinical use are going on now. The trial reportedly found no difference in 28-day mortality among 1542 patients who were randomly assigned to receive hydroxychloroquine compared with 3132 patients who received standard care (25.7 versus 23.5 percent, HR 1.11, 95% CI 0.98-1.26); there were also no differences in length of hospital stay (10). Most observational studies have also not suggested a benefit with hydroxychloroquine or chloroquine In an observational study from United States (US) concluded that hydroxychloroquine had no effect on clinical course of adult patients with COVID-19 (11). In an another observational comparative study from France, 84 patients who were given hydroxychloroquine were compared with 89 patients who were not and no differences were detected on survival without acute respiratory distress syndrome at day 21, survival on 21 days (12). Finally United States Food and Drug Administration has revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is unavailable or participation is not feasible on June,15 (13).

Hydroxychloroquine may be an alternative to remdesivir for children if remdesivir is unavailable (14). Given the lack of proven benefit, potential risks, and the revocation of the emergency use authorization, it should only be used in the context of a clinical trial. Hydroxychloroquine should be avoided in children with underlying QTc abnormalities and those who require other medications with potential for serious drug interactions with hydroxychloroquine (15).

In Turkey, hydroxychloroquine has recommended both adults and children in the treatment of COVID-19. In adult patients hydroxychloroquine has recommended for outpatient and inpatient with or without pneumonia. In children, it is recommended for COVID-19 with pneumoniae with or without azithromycin. For details, look at website of Turkish Ministry of Health for COVID-19 (16).

b. Lopinavir-ritonavir

Lopinavir (LPV) is an effective drug that inhibits the protease activity of the coronavirus. Proteinase is a key enzyme for the polyprotein synthesis of CoV. Lopinavir (LPV) is an anti-retrovirus proteinase inhibitor used since 2000 in the second-generation treatment of HIV-1 infection. In SARS-CoV and MERS-CoV diseases, LPV has been studied in vivo and in vitro and has been shown to inhibit replication. It has been shown to be effective against viral 3-chymotrypsin-like protease (3CLpro) in SARS-CoV-1. Ritonavir (RTV) increases the serum concentration of LPV by inhibiting the metabolism of LPV via the CYP3A pathway. The antiviral effect of the LPV / r combination is similar to the effect of LPV alone. LPV / R, by competing with HIV protease, causes dysregulation in the structural and functional

proteins of the virus, causing formation of immature and non-infectious virus particles and inhibition in HIV replication (17-19).

Qiu H et al. (20) evaluated 36 children (mean 8.3 years, SS 3.5 years), they gave inhaled interferons to all cases 2 times a day. In 14 cases (39%), 12 (medium-weight pneumonia, 2 were mild clinical) gave the drug LPV/R. While 19 (53%) of the patients in the study had pulmonary CT findings, others were reported to have mild clinical signs of the disease. In this study, no comparison was made between patients who were given LPV/R and those who were not. Because LPV/R treatment group mostly consists of patients with pneumonia. It was emphasized that the pediatric patients were mild or moderate, and the number of cases was low. All of the patients were recovered and discharged (20). Ye XT et al. (21) gave LPV/R treatment in 42 patients in which 47 COVID positive patients were taken. They gave inhaled interferon and arbidol tablets to remaining 5 patients. The age distribution of the patients was 5-68 years old, 9 patients were under the age of 30 and 38 patients were over the age of 30. In the patient groups they compared, the duration of the body temperature to return to normal values, WBC, lymphocyte and CRP values were found to be significantly shorter than the control group. It was observed that nCoV-RNA became negative earlier in the group treated with LPV/R. In addition, ALT and AST values were higher in the group treated with LPV/R. As the restrictive aspects of the study, the number of patients in the control group was reported to be low (21). The efficacy and safety assessment of the use of oral LPV/R (400 mg/100 mg, twice a day) of Cao et al. (22) (LOTUS China trial) in SARS-CoV-2 infection. They randomly gave LPV / r to 199 adult COVID-19 patients with severe clinics. They applied LPV/R to 99 patients and standard care to 100 patients, and LPV/R treatment did not cause a statistically significant clinical improvement compared to the control group (HR 1.24, 95% CI, 0.90-1.72), did not decrease mortality on day 28 (19.2 % 25.0%, 95% CI, -17.3-5.7) and no reduction in viral RNA detection in the throat. Viral RNA was still detected in 40.7% of the treated group at the end of treatment. Nausea, vomiting and diarrhea were more common in the group receiving LPV/R, and similar disorders were observed in the laboratory parameters between the two groups. However, the absence of a blind study, it was stated in the limitation section of the article that it was possible to be affected by the clinical condition of the patient when deciding the treatment group and whether it was observed whether steroid use was observed in patients (22). Although there are no efficacy and safety studies for the use of LPV/R in the treatment of COVID-19, it is still in the research phase. LPV/R is recommended in China 2020 COVID guide. It is recommended as an alternative drug in case of clinical worsening in children and pregnant patients (16).

It is available in the name of Kaletra © and is sold as a 200 mg / 50 mg film-coated tablet. Each tablet contains 200 mg liponavir and 50 mg ritonavir. In adult COVID-19 pregnant women, 1 tablet 2 times a day is recommended for 10-14 days, whereas 16 mg/kg/dose lopinavir dose is calculated twice a day in children between 14 days and 6 months. Between 6 months and 18 years: 15-25 kg: 200 mg 2 times a day (2x1 tablets), 26-35 kg: 300 mg 2 times a day (2x1.5 tablets),> 35 kg: 400 mg 2 times a day (2x2 tablet) oral administration has been recommended (16).

Although the drug is generally well tolerated, there may be interaction with chloroquine and hydroxychloroquine used in the treatment of COVID (http://www.covid19-druginteractions.org/) (23).

c. Favipiravir

Favipiravir is a pro-drug of ribofuranosil-5p-triphosphate (24). Its active form inhibits RNA polymerase, stopping viral replication. Most of the pre-clinical data of favipiravir was obtained from its antiviral effect against influenza and Ebola; However, the agent also shows wide activity against other RNA viruses (25).

Limited clinical experience supporting FPV use has been reported for COVID-19. In a study in which treatment was compared with lopinavir / ritonavir (LPV/R) and FPV, FPV was independently associated with faster viral clearance and a higher recovery rate in lung imaging (26). However, in another prospective, randomized, multicenter study comparing FPV and umifenovir (arbidol), clinical recovery was higher in the FPV group on the 7th day in patients with moderate COVID-19 infection (27). It has been stated in the current guideline of the Ministry of Health of the Republic of Turkey that favipiravir can be used in adult patients with severe pneumonia and / or potential / definitive COVID-19 worsening under treatment (16).

Favipiravir has a weight-dependent complex, nonlinear, time- and dose-dependent pharmacokinetics (28, 29). Since favipiravir is both metabolized and inhibited by aldehyde oxidase, initial oral loading is required to achieve adequate blood levels (24). In the current treatment guidelines, a 5-day treatment regimen is recommended in the form of 2x600 mg maintenance following the loading dose of 2x1600 mg in adult patients (16).

The plasma half-life is 4 hours. People with liver dysfunction should be monitored for blood concentration and dose adjusted. Favipiravir or its metabolites have been detected in semen and breast milk. Antibacterial agents such as piperacillin, penicillin, tazobactam, and pyrazinamide have been reported to interact with various medications, particularly antidiabetic and antihypertensives (30).

The most common side effects are diarrhea, increased serum uric acid levels, increased serum transaminases (ALT, AST, ALP) and total bilirubin levels and decreased neutrophil levels. Digestive system side effects (nausea, increased gas) and psychiatric symptoms can also be seen. It is not recommended for use in pregnancy due to its teratogenic nature. Transition

to breast milk has been reported. It is mainly excreted through the kidneys, but no dosage adjustment is recommended by the manufacturer. If a dose reduction is to be made, the loading dose is administered in the same way, but the maintenance dose can be reduced (31).

Data on the use of FVP in children is very limited in the literature and is mainly based on Ebola virus infection treatment (32). The complete maturation profiles of enzymes (mainly aldehyde oxidase) included in the metabolic pathway of favipiravir at 12 months make the drug a good candidate for treatment in children over 1 year old (33). In a study examining the use of high doses of FVP in children with Ebola virus infection, it was shown that FVP was generally tolerated and that it was not necessary to discontinue the drug due to side effects (34). It is true that extensive clinical trials are needed to routinely recommend the use of FVP in children in COVID-19 infection.

d. Remdesivir

Remdesivir is intracellularly metabolized from a prodrug of a nucleotide analogue to an analogue of adenosine triphosphate which inhibits viral RNA polymerases. Remdesivir has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses which has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV] (35-39). Remdesivir has activity against SARS-CoV-2 shown with in vitro testing . It was stated that remdesivir has a favorable clinical safety profile, with reports on the basis of experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection (39-41). There is a recent study evaluating patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, in which clinical improvement was observed in 36 of 53 patients (68%) (41). A multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) included 1059 patients with confirmed COVID-19 and evidence of lung involvement; 89 percent had severe disease and 26 percent were receiving invasive mechanical ventilation or ECMO at baseline (42). According to a preliminary report, remdesivir resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care (median 11 versus 15 days with placebo; rate ratio for recovery 1.32, 95% CI 1.12-1.55). In contrast, in a double-blind randomized trial in China of 237 patients with severe COVID-19 (hypoxia and radiographically confirmed pneumonia), time to clinical improvement was not statistically different with remdesivir compared with placebo for 10 days (median 21 versus 23 days; HR for improvement 1.23 [95% CI 0.87-1.75]) (43).

Also there is a planned phase II/III clinical trial of remdesivir to treat paediatric patients hospitalised with Covid-19 to assess the safety, tolerability, pharmacokinetics and efficacy of remdesivir in around 50 paediatric patients suffering from moderate-to-severe Covid-19, including newborns and adolescents, at more than 30 sites across the US and Europe.

But still measurement of efficacy requires further randomized, placebo-controlled trials of remdesivir therapy.

4. Convalescent Plasma

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a potential therapy for COVID-19.

In an open-label trial from China, 103 patients with life-threatening or severe (on invasive COVID-19 were randomly assigned to receive standard treatment with or without convalescent plasma (44). Although convalescent plasma improved the rate of nasopharyngeal viral RNA clearance at 72 hours compared with standard treatment alone (87 versus 38 percent), there were no statistically significant differences in the overall rates of clinical improvement or mortality by 28 days. Among the subset of patients who had severe but not life-threatening disease, the rate of clinical improvement was greater with convalescent plasma (91 versus 68 percent)

In Cochrane study, eight studies was included(seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised. It was stated that there is uncertainity whether convalescent plasma is effective for people admitted to hospital with COVID-19 as studies reported results inconsistently, making it difficult to compare results and to draw conclusions (45).

5. Tocilizumab

Tocilizumab is an IL-6 receptor inhibitor used for rheumatic diseases and cytokine release syndrome and is being evaluated in randomized trials for treatment of COVID-19. Elevated interleukin 6, C–reactive protein (CRP), and ferritin, have been shown to be higher in patients with severe COVID–19 and predictors of mortality (46,47). In one study, in critically ill COVID–19 patients who required mechanical ventilation or vasopressor support compared to those with milder disease, the level of interleukin 6 was noted to be 10 times higher and interleukin 6 level correlated with the detection of COVID-19 RNAaemia (48). These findings suggest that anti–cytokine targeted therapies might be of benefit for patients with severe COVID–19. In a study, tocilizumab cohort had a higher rate of improvement in oxygen–support category for both subsets of patients who required invasive and non–invasive oxygen support. Among intubated patients, tocilizumab cohort had 5 days shorter median time to clinical improvement and

the median duration of vasopressor support and invasive mechanical ventilation were both 3 days shorter in tocilizumab cohort compared to no tocilizumab cohort. Overall, median length of stay in hospital was 4 days longer in tocilizumab cohort but it was stated that importantly higher proportion of these patients required admission to intensive care unit (49).

It was also noted that previous studies suggested that SARS–CoV–2 can cause over–activation of immune system and clinicians need to be vigilant against cytokine release syndromes (50). Measurement of inflammatory biomarkers may guide clinicians to select appropriate patients for immunosuppressive therapy .

In a preliminary report evaluating tocilizumab for treatment of severe COVID-19 patients, tocilizumab administration did not reduce ICU admission or mortality rate in a cohort of 21 patients (51). These studies show that additional data are needed to understand the effect(s) of tocilizumab in treating patients diagnosed with COVID-19.

Sarilumab and siltuximab are other agents that target the IL-6 pathway and are also being evaluated in clinical trials.

CONCLUSION

There is a growing need for well-designed controlled clinical trials to better define the safety and efficacy of potential treatments for COVID-19 in children.

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Personnel Protective Equipment for Healthcare Professionals During COVID-19 Pandemic

COVID-19 Pandemisi Sırasında Sağlık Çalışanları İçin Kişisel Koruyucu Ekipmanlar

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ABSTRACT

COVID-19 is highly contagious and transmission dynamics of COVID-19 are not yet fully elucidated. It is known that the ill person begins to become contagious before the symptoms of the disease begin. Also asymptomatic person who are infected but does not have symptoms and signs, can infect other individuals. The only way for health workers to protect themselves from COVID-19 is proper use of personal protective equipment and to ensure hand hygiene. COVID-19 is transmitted through close contact and large respiratory droplets and not transmitted by airborne. The surgical mask prevents the passage of respiratory droplets. However, during the aerosol producing procedures performed on the patient, small particles containing infectious particles are scattered to air in high amounts. Healthcare workers are more likely become infected during these procedures. It is recommended to wear respirator during these procedures. Use of masks or respirators must be in conjunction with other recommended PPE and appropriate hand hygiene.

Key Words: COVID-19, Personnel Protective Equipment, Pandemic, Healthcare worker

ÖZ

COVİD-19 oldukça bulaşıcı bir vürüstür ve bulaş dinamikleri henüz tam olarak aydınlatılabilmiş değildir. Hasta kişinin semptomlar başlamadan önce bulaştırıcı olmaya başladığı bilinmektedir. Ayrıca enfekte olmuş ancak semptom ve bulguları olmayan asemptomatik bireylerin de diğer kişileri enfekte edebildiği bilinmektedir. Sağlık çalışanlarının COVID-19 hastalarına bakım verirken kendilerini korumalarının tek yolu el hijyenlerini sağlamaları ve kişisel koruyucu ekipmanları (KKK) doğru şekilde kullanmalarıdır. COVID-19 yakın temasla ve büyük solunum damlacıkları ile bulaşmaktadır, hava yolu ile bulaşmamaktadır. Cerrahi maske solunum damlacıklarının geçişini önlemektedir. Ancak aerosol oluşturan işlemler sırasında enfeksiyöz küçük partiküller yüksek oranda çevreye saçılır. Bu işlemler sırsında sağlık çalışanlarının enfekte olma ihtimali daha yüksektir ve bu nedenle bu işlemler sırasında respirator takılması önerilir. Sağlık çalışanlarının kendilerini korumaları için, maske ve respirator kullanımının yanısıra diğer önerilen KKK'ler de kullanılmalı ve el hijyeni sağlanmalıdır.

Anahtar Kelimeler: COVID-19, Kişisel koruyucu ekipmanlar, Pandemi, Sağlık çalışanı

INTRODUCTION

Health workers are at the forefront of the fight against COVID-19 infection. The only way for health workers to protect themselves is proper use of personal protective equipment (PPE) and to ensure hand hygiene (1). The transmission dynamics of the new COVID-19 infection are not yet fully elucidated. By the time the available information suggests the infection is transmitted through close contact and large respiratory droplets and not transmitted by airborne. It is known that the ill person begins to become contagious before the symptoms of the disease begin. It is also known that asymptomatic person who are infected but does not have symptoms and signs, can infect other individuals

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(2). Considering all this information, health workers should use the right PPE in the right situation and at the right time.

What is personal protective equipment:

1. Surgical mask
2. N95/FFP2 respirator (or N99)
3. Apron
4. Glove
5. Goggles or face shield
6. Overshoes

Mask

Healthcare professionals who care for possible or definite COVID-19 patients should always wear masks. There are two main types of mask:

Medical (surgical) mask: It acts as a physical barrier in front of the mouth and nose. If worn properly, the surgical mask prevents the respiratory droplets of the sick person from spreading to the mouth and nose of the healthcare worker. The surgical mask does not filter or block very small particles that can be transmitted by coughing, sneezing, or some medical procedures in the air. Also, the surgical mask may not provide complete protection if it does not fit the face properly (3).

Respirators: They are also referred to as N95, N99 or FFPII, FFPIII. N95 masks, fits completely on the face and have the ability to filter very effectively the respiratory particles. The expression N95 means that at least 95% of very small (0.3 micron) particles are filtered by the mask. If used correctly, the filtering properties of N95 respirators are higher than medical masks (3).

Important points to be considered while wearing a mask: The recommendations regarding which mask should be worn in which cases is summarized in Table I (2,4). IDSA says that healthcare professionals can wear surgical or N95 (or N99) masks, since wearing surgical or N95 masks is superior to approaching possible or definitive COVID-19 patients without a mask. Use of masks or respirators must be in conjunction with other recommended PPE and appropriate hand hygiene (1,2). The recommendations for PPE are shown in Table I (2,4).

There are necessary points to be considered while wearing a mask. The medical mask should be worn to cover the nose, mouth, and the lower part of the chin and must be tightly tied. Stranded flexible tape on the bridge of the nose should be compressed. Medical masks should be changed with new ones in case of contamination, moisture, wear (3,5).

Respirator fit test should be done when using a respirator. Respirators can be used for up to 4-6 hours as long as they are not damaged, moisturized and become dirty (4). Regardless of the mask type, healthcare providers must maintain hand hygiene before and after touching the mask (3).

Apron

Healthcare professionals who will be closer than 1 meter in contact with the probable or definite COVID-19 patients should wear apron. The apron should be knee-length and cover the front and back of entire body. The sleeves of the apron should be long and have wristbands (5).

Gloves

Healthcare professionals who will be closer than 1 meter in contact with the probable or definite COVID-19 patients should wear gloves. Gloves should be worn to cover the wrist part of

Table I: Recommendation for PPE (2,4).

Activities	Surgical mask	Respirator	Gloves	Gown	Goggles/ face shield	Boots or closed work shoes or overshoes
Healthcare workers when providing direct care in patient room	√	X	√	√	√	X
Healthcare workers when aerosol-generating procedures performed on COVID-19 patients	X	√	√	√	√	X
Cleaners when entering the room of COVID-19 patients	X	√	√	√	√	√
Healthcare workers in an ambulance or transfer vehicle for COVID-19 patient	X	√	√	√	√	X
Healthcare workers in outpatient facilities	√	X	√	√	√	X
Cleaners after and between consultations of patients with respiratory symptoms in outpatient facilities	√	X	√	√	X	√
Patient with respiratory symptoms in waiting room	√	X	X	X	X	X
Laboratory personnel Working with respiratory samples	X	√	√	√	√	X

the apron (5). There is no recommendation for health personnel about double-gloving (2).

Goggles or face shield

The transmission through the eye for COVID-19 is possible. Goggles or face shield should be used to cover the face and eyes (4).

Overshoes

There is no recommendation for wearing overshoes. However, if there is a risk of splashing of contaminated fluids on the health care worker, overshoes can be used (2).

Other important points:

Aerosol producing procedures: COVID-19 infection is transmitted by respiratory droplets and the surgical mask prevents the passage of respiratory droplets. However, during the various procedures performed on the patient, small particles containing infectious particles are scattered to air in high amounts. After these processes, COVID-19 virus in aerosol particles has been reported to hang up to 3 hours in the air (4). Healthcare workers are more likely become infected during these procedures. It is recommended to wear N95 or N99 during these procedures (1,2,4,5). These processes are listed below (4):

- Aspiration of respiratory secretions
- Collection of respiratory tract specimens
- Intubation, extubation and related procedures,
- Dentistry applications
- Highflow nasal oxygen
- Noninvasive ventilation, bi-level positive airway pressure (BiPAP) and continuous positive airway pressure ventilation (CPAP)
- High-frequency oscillating ventilation
- Cardiopulmonary resuscitation
- Drug treatment with nebulizer
- Bronchoscopic and endoscopic procedures

Sequence for putting on PPE: Hand hygiene should be provided before wearing PPE. The order for putting on PPE is apron, mask, goggles/face protector and gloves (5,6).

Sequence for removing PPE: The order for removing PPE is gloves, apron, goggles/face protector, mask. Hand hygiene should be provided after removing the apron. When removing goggles/face protector, front side should not be touched. Finally the mask is removed and hand hygiene is provided again. It is especially important to remove the mask after leaving the patient's room (5,6).

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Tıbbi Mikrobiyoloji Laboratuvarı Açısından SARS-CoV-2

SARS-CoV-2 in Terms of Medical Microbiology Laboratory

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ÖZ

Coronaviridae ailesinde yer alan koronaviruslar (CoV), vahşi ve evcil hayvanlarda farklı şiddette gastrointestinal, respiratuvar ve sistemik hastalıklara neden olurken, insanlarda bağışıklık durumuna göre soğuk algınlığından pnömoniye kadar farklı klinik tablolara yol açabilir. Günümüze dek insanlarda enfeksiyon etkeni olarak yedi koronavirus türü tanımlanmıştır; bunlardan HCoV 229E, HCoV NL63, HCoV HKU1 ve HCoV OC43, tipik olarak immünokompetan bireylerde soğuk algınlığı semptomlarına neden olurken, SARS-CoV (Ciddi Akut Solunum Sendromu Koronavirus), MERS-CoV (Orta Doğu Solunum Sendromu Koronavirus) zoonotiktir ve ciddi solunum yolu hastalıklarına ve ölümlere neden olur. Çin'in Hubei Eyaleti, Wuhan kentinde Aralık 2019'da başlayan ve kısa sürede pandemi olarak tanımlanan COVID -19'un etkeni SARS-CoV-2 insanlarda enfeksiyon etkeni olarak tanımlanan yedinci koronavirustur. Dünya Sağlık Örgütü(DSÖ)'nün SARS-CoV-2 kaynaklı COVID-19'u pandemi olarak tanımlaması ve dünya üzerinde her geçen gün vaka ve ölüm sayılarının artmasından dolayı, aşı çalışmaları için virusun yapısı ve salgını kontrol etmede en önemli basamak olan viral tanı yöntemlerinin kullanılması daha da önem kazanmıştır.

Anahtar Sözcükler: Koronavirus, SARS-CoV-2, Tanı

ABSTRACT

Coronaviruses (CoV), which are in the *Coronaviridae* family, cause different severity of gastrointestinal, respiratory and systemic diseases in wild and domestic animals, and can lead to different clinical manifestations, ranging from colds to pneumonia, depending on immunity. To date, seven types of coronavirus have been identified as infectious agents in humans; of these, HCoV 229E, HCoV NL63, HCoV HKU1 and HCoV OC43 typically cause cold symptoms in immunocompetent individuals, while SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) is zoonotic and cause severe respiratory diseases and deaths. SARS-CoV-2, the causative agent of COVID-19, is the seventh coronavirus identified as an infection agent in humans, which started in December 2019 in Wuhan, Hubei Province of China and was identified as a pandemic in a short time. Since the World Health Organization (WHO) defines SARS-CoV-2-sourced COVID-19 as a pandemic, and because of the increasing number of cases and deaths worldwide, structure of the novel virus and viral diagnosis methods gained importance respectively for vaccine studies and for controlling the outbreak caused by the virus.

Key Words: Coronavirus, SARS-CoV-2, Diagnosis

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GİRİŞ

Aralık 2019'da Çin'in Hubei Eyaleti Wuhan şehrinde etiyolojisi tespit edilmeyen vakaların Dünya Sağlık Örgütü (DSÖ)'ne bildirilmesiyle başlayan çalışmalar daha sonraki dönemde pandemi olarak tanımlanacak olan süreci başlattı. DSÖ 12 Ocak 2020'de etkeni 2019 yeni Koronavirus (novel Coronavirus, 2019- nCoV), takiben 12 Şubat 2020'de etkenin neden olduğu hastalığı ise COVID-19 olarak adlandırdı. Daha sonra etken, Uluslararası Virus Taksonomisi Komitesi (International Committee of Taxonomy of Viruses, ICTV) tarafından SARS-CoV-2 olarak isimlendirildi (1). Bu derlemede 22 Mayıs 2020 tarihi itibariyle dünyada 216 ülkede, 4.962.707 konfirme edilmiş vaka ve 326.459 kişinin ölümüne yol açtığı bildirilen SARS-CoV-2'nin mikrobiyolojik özellikleri ve tanı yöntemleri ele alınmıştır (2).

KORONAVİRUSLAR- GENEL BAKIŞ

Koronoviruslar *Nidovirales* takımında, *Coronaviridae* ailesinin *Coronavirinae* alt ailesinde yer alırlar. Sekans özellikleri ve filogenetik ilişkilerine göre Coronavirinae alt ailesi dört cinse ayrılır; Alfakoronaviruslar, Betakoronaviruslar, Gamakoronaviruslar ve Deltacoronaviruslar. Gammacoronaviruslar ve Deltakoronaviruslar bazı memeli türleri ve kuşları enfekte ederler ancak insanlarda hastalık oluşturmazlar (3). Ancak Alfakoronavirus ve Betakoronavirus cinsleri insanlarda solunum yolu enfeksiyonundan, bazı hayvan türlerinde de gastrointestinal sistem enfeksiyonlarından sorumludur. Aralık 2019 tarihine kadar insanlarda enfeksiyon etkeni olan (Human Coronavirus-HCoV) altı Koronovirus cinsi tanımlanmıştır. Bunlar HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV ve MERS-CoV'dur. HCoV-229E ve HCoV-NL63 Alphacoronavirus cinsi içinde yer alırken, HCoV-OC43, HcoV-HKU1, SARS-CoV ve MERS-CoV Betakoronavirus cinsinde yer almaktadır (3).

2002 yılına kadar insanlarda enfeksiyona neden olan sadece iki tip HCoV biliniyordu; bunlar 1960'larda üst solunum yolu enfeksiyonu olan kişilere ait örneklerin hücre kültüründen izole edilmiş olan HCoV-229E ve HCoV-OC43'dü. Yaygın olarak dolaşımda olan diğer Koronoviruslar, HCoV-NL63 ve HCoV-HKU1 ise 2000'li yılların başında bronşiolit ve pnömoni kliniği olan kişilerden izole edilmiştir (4).

2002 yılının sonlarında da güney Çin'in Guangdong eyaletinden yayılan, yarasa kaynaklı bir Betacoronavirus olan Ciddi Akut Solunum Sendromu ile İlişkili koronovirus, SARS-CoV tanımlanmıştır (5). SARS-CoV enfeksiyonu yaklaşık 30 ülkede görülmüş ve 8273 kişinin enfekte olması ve 774 kişinin ölümüyle sonuçlanmıştır (6).

2012 yılında yine bir Betakoronavirus tek hörgüçlü develerden Suudi Arabistan'da insanlara yayılmış ve Orta Doğu Solunum Sendromlu Koronavirus (MERS-CoV) adını alarak SARS ile benzer bir klinik sendroma neden olmuştur. MERS-CoV yaklaşık 27 ülkede, 2500 kişinin enfekte olması ve 858 ölümle sonuçlanan, 60 yaş üzeri popülasyonda mortalitenin yüksek seyrettiği, ileri yaş, erkek cinsiyet ve kronik hastalık varlığının kötü prognozda etkili kabul edildiği bir tablo ile sonuçlanmıştır (7,8).

İnsanlarda ortaya çıkan en son Koronovirus, Aralık 2019'da Çin'in Hubei Eyaleti, Wuhan Şehrinde ortaya çıkmış, hastalardan alınan solunum yolu örneklerinin incelenmesiyle virusun daha önceki SARS-CoV ile taksonomik olarak ilişkili olduğu anlaşılmıştır. Önceleri Novel Koronavirus (2019-nCoV), olarak adlandırılan virusa Uluslararası Virus Taksonomisi Komitesi'nde (ICTV) bir çalışma grubunun önerisiyle SARS-CoV-2, SARS-CoV-2 kaynaklı enfeksiyonlara ise COVID-19 adı verilmiştir. Vakaların patlamasıyla süreç 11 Mart 2020'de DSÖ tarafından pandemi olarak ilan edilmiştir (9).

SARS-CoV-2; GENEL YAPISI VE REPLİKASYONU

Coronaviridae ailesi, zarflı, pozitif polariteli, tek iplikçikli RNA genomuna sahip viruslardan oluşmaktadır ve SARS-CoV-2'nin genel yapısı, *Coronaviridae* ailesindeki diğer viruslara benzer. SARS-CoV-2 yaklaşık 60-140 nm çapında, protein yapıda çıkıntıları olan, viral genom uzunluğu yaklaşık 30 kb olan, tek sarmallı pozitif polariteli zarflı bir virustur (10-12). Sekans analizleri sonrasında SARS-CoV-2'nin Betakoronavirus 2b soyunda yer aldığı, nükleotid dizisi olarak SARS-CoV ile %79.0, MERS-CoV ile %51.8 ve yarasa SARS benzeri Koronovirus izolatı (Bat-SL-CoVZC45) ile %87.6-%89 benzerlik gösterdiği saptanmıştır (11, 13, 14).

RNA viruslarının genelinde olduğu gibi enfekte ettiği hücrelerin sitoplazmasında replikasyonunu gerçekleştiren virus, pozitif polariteli olduğu için viral genomun, direkt kalıp olarak kullanılmasıyla çeşitli yapısal ve yapısal olmayan proteinler kodlar. Koronoviruslarda viral genomun değişken sayıda (6-11 arasında) açık okuma çerçevesi (open reading frame, ORF) içerdiği gösterilmiştir. Viral RNA'nın üçte ikisini oluşturan ilk ORF'ler (ORF1a/b) 16 adet yapısal olmayan protein kodlarken, (nsp 1-16), genomun kalan üçte birini oluşturan diğer ORF bölgelerinden, en az dört adet yapısal protein; spike-çıkıntı (S) glikoprotein, envelope-zarf (E) proteini, matriks (M) proteini ve nükleokapsid (N) proteini ve konak immun cevabıyla etkileşen birkaç aksesuar protein kodlanır (15, 16).

SARS-CoV-2 proteinlerinin işlevleri daha önceden bilinen Coronovirusların proteinleri temel alınarak açıklanmaktadır. Yapısal olmayan proteinlerin çoğunun viral replikasyondaki görevi tanımlanmış olmakla birlikte, bazı yapısal olmayan proteinlerin görevi henüz netlik kazanmamıştır. Dört yapısal protein;

S proteini; virus yüzeyinde, viral zarfın üzerinde çıkıntılar şeklinde olup, virusun reseptöre bağlanma ve membran füzyonu ile konak hücreye tutunmasını sağlamaktadır. S proteini konak hücre tropizmini belirleyen önemli viral proteindir. S proteininin S1 ve S2 ilmekleri vardır; S1 temel olarak virusun konak hücre reseptörüne bağlanmasından, S2 ise membran füzyonundan sorumludur. SARS-CoV ve SARS-CoV-2 S1 proteini içerisinde

50 adet korunmuş proteine sahiptir. Bu veriler SARS-CoV-2'nin de SARS-CoV'da olduğu gibi anjiyotensin dönüştürücü enzim 2'yi (ACE 2) reseptör olarak kullanabileceğini düşündürmektedir (17-20). ACE 2, akciğerler, mide, ince bağırsak, kolon, cilt, lenf düğümleri, karaciğer safra kanalları, böbrek parietal epitel hücreleri ve beyindeki arteriyel ve venöz endotelyal hücrelerde ve arteriyel düz kas hücrelerinde bulunur, ayrıca akciğer alveoler epitel hücrelerinin yüzeyinde ve ince bağırsağın enterositlerinin yüzeyinde eksprese edilir (21).

S proteini koronavirüs enfeksiyon patogenezinde ve ilaç/aşı geliştirilmesi için hedef olabilmesi açısından önemli yere sahiptir.

M proteini; viral partikül oluşumu ve salınımda çok önemli rolü olan zarf proteinleridir. Üç adet transmembran bölümü vardır ve virionları (Virion=tam virus partikülü) şekillendirir ve nükleokapside bağlanır. Nükleokapsid proteininin stabilizasyonunu sağlar. Böylece nükleokapsid-RNA kompleksinin oluşumu ve devamını sağlar. Virus hücre içi dengesinin sağlanmasında önemli rol oynar. Konak hücrenin virüs tarafından duyarlı hale getirilmesinde bu protein önemli rol alır (22).

E proteini; viral parçaların bir araya getirilmesi (assembly), virus salınımı ve rolü tam olarak bilinmemekle birlikte patogenezde rol oynar. E proteini, virusun tomurcuklanarak hücreden ayrılmasında rol oynayan önemli bir virulans faktörüdür (23).

N proteini; M protein ile birlikte viral partikül oluşumu ve salınımda çok önemli rolü olan zarf proteinleridir. Viral RNA'nın replikasyon ve transkripsiyonunun düzenlenmesinde rol oynar. N proteini ayrıca, interferon antagonisti olarak davranır, böylece virusun immün sistem tarafından yok edilmeye çalışılması da inhibe edilmiş olur (24, 25).

SARS-CoV-2'nin konak hücrelerdeki replikasyonu, S proteini aracılığıyla hücresel anjiyotensin dönüştürücü enzim 2 (ACE 2) reseptörüne bağlanmasıyla başlar. Virusun hücre içine girişiyle birlikte öncelikle genomik RNA kalıp olarak kullanılarak poliprotein 1a/1ab translasyonu gerçekleşir ki, buradan replikasyon-transkripsiyon kompleksini (RTK) oluşturmak üzere yapısal olmayan proteinler kodlanır. RTK yapısal proteinlerin replikasyonundan sorumludur. S, E ve M proteinleri endoplazmik retikulum (ER) ve Golgi aparatına girer ve N proteini, bir nükleoprotein kompleks oluşturmak için pozitif iplikçikli genomik RNA ile birleştirilir. Bu yapısal proteinler daha sonra ER'den Golgi aparatı yoluyla küçük veziküller aracılığıyla taşınacak olan virion öncüsü ile kaynaşırlar. Virionlar daha sonra enfekte olmuş hücreden ekzositoz yoluyla salınır ve enfekte ederek replike olmak için başka bir konakçı hücre arar (26).

TANI

SARS CoV-2 virusunun etkeni olduğu COVID-19 enfeksiyonlarının henüz kesin bir tedavisi ve etkili bir aşısı bulunmamaktadır. Bu nedenle hasta yönetiminin en doğru şekilde yapılabilmesi ve pandeminin kontrol altına alınabilmesi için doğru ve hızlı tanının yapılması çok önemlidir.

Doğru tanı için en önemli nokta ise, hasta örneğinin doğru zamanda, doğru yerden ve doğru şekilde uygun ekipmanla alınarak uygun koşullarda (süre, ısı) laboratuvara ulaştırılmasıdır.

SARS-CoV-2'nin moleküler mikrobiyolojik tanısında örnek alımı için en uygun zaman, semptomların başlamasından sonraki ilk 5-7 gündür, zira yedinci günden sonra üst solunum yollarından alınan örneklerde sonucun pozitif çıkma olasılığı düşmekte, testin duyarlılığı azalmaktadır. Nükleik asit amplifikasyon testleri (NAAT) için alınabilecek üst solunum yolu örnekleri; nazofaringeal/orofaringeal sürüntü, nazofaringeal aspirat örnekleri, alt solunum yolu örnekleri ise; bronkoalveoler lavaj (BAL), bronşiyal yıkama, balgam, trakeal aspirat, transbronşiyal akciğer biyopsi örnekleridir. Test duyarlılığı açısından bronkoalveoler örnekler uygun olmakla birlikte, örnek alan kişi için yüksek risk taşıdığından rutinde çok tercih edilmemektedir. İdeal olarak nazofaringeal ve orofaringeal sürüntünün birlikte alınarak aynı viral transport besiyeri (VTM) içine konulması ve bu şekilde laboratuvara gönderilmesi önerilmektedir. Nazofaringeal örnekler için NAAT çalışırken inhibisyona neden olduğundan kesinlikle pamuk uçlu eküvyonlar önerilmez. Rayon veya dakron uçlu eküvyonlarla örnek alınmalıdır. Tüm solunum yolu örnekleri için geçerli olmakla birlikte, özellikle alt solunum örnekleri alınırken kişisel koruyucu ekipmanların (KKE) kullanılması önem arz etmektedir. Örnekler alındıktan sonra üçlü biyolojik taşıma kapları içinde, en kısa sürede laboratuvara ulaştırılmalı; hemen laboratuvara gönderilemeyecek örnekler +4 ^{o}C'de bekletilerek (48 saaatte kadar) laboratuvara ulaştırılmalıdır (27).

Genel olarak enfeksiyon etkenlerinin mikrobiyolojik tanısında etkenin kendisi ya da bir antijenini saptayan direkt testler ve konağın etkene karşı geliştirdiği özgül antikor yanıtını gösteren indirekt testler kullanılır. Bugün için SARS-CoV-2 rutin tanısında Dünya Sağlık Örgütü (DSÖ) öncelikli olarak 'real time reverse transcriptase polymerase chain reaction (rRT-PZR)' yöntemini kullanan testleri önermekle birlikte, diğer yöntemleri esas alan farklı testler de geliştirilmeye devam etmektedir.

1. Hücre kültürü

İnsan Koronoviruslarının (HCoV) hücre kültüründen tanı amaçlı izolasyonu permisif hücre hatlarının yetersizliği, sonuçlanma süresinin uzunluğu, yoğun uğraş ve uzman ekip gerektirmesi ve kültürün doğrulanması için gerekli antiserumların eksikliğinden dolayı rutin olarak uygulanmamaktadır (28). SARS-CoV, MERS-CoV ve SARS-CoV-2 primer maymun hücrelerinde ve Vero ve LLC-MK2 gibi hücre hatlarında üremekte fakat şüpheli olguların tanısında rutin tanı laboratuvarlarında biyogüvenlik şartları nedeniyle yapılması önerilmemektedir. Bununla birlikte elde edilen izolatların özelliklerinin tanımlanmasında ve aşı ve terapötik ajanların geliştirilmesinde virusun üretilmesi kritik önem taşımaktadır (29,30).

2. Dizi analizi

Şüpheli pozitif sonuçların doğrulanmasında virus kaynağının belirlenmesi, yayılma yollarının izlenmesi, zaman içinde virusun uğradığı değişikliklerin tanımlanarak bulaşıcılık, reseptöre tutunma, virulans, tedavi seçenekleri gibi enfeksiyon parametrelerini etkileyebilecek mutasyonların belirlenmesini sağlayacağından, düzenli aralıklarla elde edilen örneklerden virus genetik diziliminin analizlerinin yapılması önerilmektedir (31,32).

3. Nükleik asit amplifikasyon testleri (NAAT)

SARS CoV-2 virusu ile enfekte hastalarda gözlenen semtomlar nonspesifiktir ve bunların çoğu diğer solunum sistemi enfeksiyonlarında da izlenmektedir. Enfeksiyonun tanısında virusa yönelik olarak en yaygın yöntem moleküler testlerdir. Moleküler tekniklerin geliştirilmesi patojenin proteomik ve genomik kompozisyonunun ya da enfeksiyon sırasında ve sonrasında konaktaki protein/genlerin ifadelerindeki değişikliklerin anlaşılmasına bağlıdır (33). Virusun ilk sekans analizi metagenomik RNA dizileme yöntemi ile yapılmış ve bulgular resmi olarak açıklandıktan sonra dizileme 10 Ocak 2020 tarihinde GenBank sekans bilgi havuzuna eklenmiştir. Dünya Sağlık Örgütü ve Çin'in ortak raporuna göre, Aralık 2019-Şubat 2020 tarihleri arasında 104 suş izole edilmiş ve dizilemesi yapılmıştır. Genom dizileme, primer ve probe tasarlamada ve diğer nükleik asit testlerinin geliştirilmesinde araştırmacılar için en önemli ihtiyaçtır (34,35).

SARS CoV-2'yi genetik olarak saptayabilecek çok sayıda rRT-PZR kiti tasarlanmaktadır. RT-PZR yöntemi ile viral RNA'dan ilk önce komplementer DNA (cDNA) elde edilmekte ve ardından cDNA'daki spesifik bölgelerin çoğaltılması sağlanmaktadır. Test tasarımı genellikle iki ana basamaktan oluşur. İlk olarak, genom dizisi hizalanır ve RNA'nın çoğaltılması için en uygun primer tasarımı yapılır. Ardından yöntem optimize edilir ve test geliştirilir (36). Corman ve ark. (37), etkeni saptamada kullanılabilecek 3 adet en iyi korunan gen dizisini göstermiştir. Bunlar:

1. ORF1ab bölgesinde RdRp (RNA bağımlı RNA polimeraz) geni,
2. Zarf (E 'Envelope') protein geni
3. Nükleokapsid (N) protein geni.

İlk 2 gen etkeni saptamada daha yüksek analitik duyarlılık göstermiştir. Bundan sonraki aşamada yöntemin optimizasyonu (kullanılacak reaktifler, test inkübasyon zamanı ve ısı gibi) geliştirilmiştir (37).

Günümüzde çok sayıda nükleik asit ve antikor saptama kitleri tanıda kullanılmak üzere onay almış olmakla birlikte, RT-PZR solunum yolları örneklerinde etkenin saptanması için en yaygın kullanılanıdır. Hastalık Kontrol ve Önleme Merkezi (CDC), SARS CoV-2 varlığını saptamada tek basamaklı rRT-PZR yöntemini kullanmaktadır. Uygulamada viral RNA örnekten ekstrakte edilmekte ve ardından master miks bileşeni eklenmektedir. Master miks bileşeni içinde nükleaz içermeyen su, iki adet primer (forward ve reverse), floresan özellikli bir probe ve enzim, magnezyum, nükleotidler gibi bileşenlerden oluşan bir reaksiyon içeriği bulunmaktadır. Master miks ve RNA bir ısı döngü cihazına yüklenir ve tanımlanan ısılarda ve sürelerde reaksiyon gerçekleştirilir. Test sürecinde bir örnekteki RNA'nın çoğalması eş zamanlı olarak floresan sinyalin görülmesi ile saptanır. Sonuçların doğru yorumlanması için her testte pozitif ve negatif kontrollerin kullanılması gereklidir. SARS CoV-2 için CDC, nCoVPC olarak isimlendirilen pozitif kontrol sağlamıştır (38).

Dünya Sağlık Örgütü (DSÖ) 2 Mart 2020 tarihinde yayımladığı geçici rehberde, COVID-19 salgınında tanı testlerinin farklı bulaş senaryolarında ne şekilde uygulanabileceğine dair bir algoritma belirlemiştir. Buna göre virusun dolaşımda olmadığı ülkelerde ilk olgunun tanısının doğrulanması için ilk aşamada virus genomunda en az iki farklı bölgeyi hedefleyen NAAT testi ile alınan pozitif sonucun ardından virusun kısmi ya da tüm genom dizilmesinin yapılması, SARS-CoV-2'nin yaygın olarak görüldüğü ülkelerde ise tek ayırt edici bir hedef bölge kullanarak RT-PZR ile tarama yapılması önerilmiştir. Ancak bir ya da daha fazla negatif sonuç enfeksiyon olasılığını dışlamayacaktır (39).

Gerçekte RT-PZR testleri, uzun sonuçlanma süreleri, yoğun uğraş-özel ekipman-tecrübeli personel gerektirmesi, pahalı olması ve kontaminasyon riski gibi çok sayıda kısıtlamalara sahiptir. Metodolojik nedenlerinin yanı sıra etken ve enfeksiyonun patogenezine bağlı olarak da negatif sonuçlar alınmaktadır. Örnekteki materyalin niteliği, enfeksiyonun erken ya da geç döneminde örnek alınması, örneğin uygunsuz transportu ya da testin doğasından kaynaklanan teknik nedenler (örn; virus mutasyonu, testte inhibisyon) testin sonucunu etkilemektedir (31). Alt solunum yolu enfeksiyonu ile izole edilen hastalarda başlangıçta negatif ya da zayıf pozitif bulunan PCR testleri ile, sonraki testlerde pozitif sonuç alındığı gösterilmiştir (40).

Çeşitli çalışmalarda asemptomatik hastaların virusu yayabileceği ve PZR testi ile pozitif sonuç alındığı gösterilmiştir. Ayrıca klinik semptom ve radyolojik bulguları olmayan, 2 negatif PCR test sonucu ile taburcu ya da karantinadan çıkarılan hastalarda 5-13 gün sonra PZR testinde pozitiflik saptandığı rapor edilmiştir (41).

Küçük prospektif bir çalışmada, farklı örneklerde viral yük araştırmaları yapılmış, semptomatik ve asemptomatik hastalarda benzer düzeyde bulunmuştur (42). Başka bir çalışmada boğaz sürüntüsü ve balgam örneklerinde semptomlar başladıktan sonra 5-6. günlerde viral yükte 10^4–10^7 kopya/ml düzeylerinde pik gösterilmiş ve erken ve ilerleyici evrelerde iyileşme dönemine göre daha yüksek seyrettiği belirlenmiştir (43). Viral yükün hastalığın ciddiyeti ve prognozu açısından belirleyiciliği henüz net olmamakla birlikte yüksek viral yüke sahip hastaların bulaştırıcılık oranlarının da yüksek olacağı kuvvetle muhtemeldir.

SARS CoV-2 RNA için yüksek derecede spesifik ve diğer koronavirüslerle çapraz reaksiyon oluşturmayan bir RT-

PZR testi Ocak 2020 ikinci yarısında Tib-Molbiol tarafından geliştirilmiştir. Bu test virus RNA'sını E ve RdRp genleri aracılığı ile saptamaktadır. E geni ilk taramada kullanılırken RdRp geni doğrulamada kullanılmıştır (44). Diğer bir yaklaşımda virusun ORF1b ve N bölgeleri tek basamaklı RT-PZR yöntemi ile 1 saat 15 dakikada saptanmaktadır. Bu yöntemde N geni taramada, ORF1b ise etkenin doğrulanmasında kullanılmıştır. Ancak bu test SARS CoV ve diğer yakın ilişkili viruslar ile de pozitif sonuç verebildiğinden araştırmacılar pozitif sonuçların dizi analizi ile ayırt edilmesi gerektiğini ifade etmişlerdir (45).

RT-PCR testinin dışında izotermal çoğaltma olarak isimlendirilen yöntemi kullanan nükleik asit testleri de geliştirilmektedir. Bunlardan en dikkat çekici olanlarından XpertÒ Xpress SARS CoV-2 (Cepheid,ABD), 45 dakikada sonuç verebilen tezgah üstü bir sistemdir. Hızlı ve otomatize hasta başı uygulanan bu moleküler test ile SARS CoV-2 virusu nazofarengeal sürüntü, yıkama ya da aspirat örneklerinde kalitatif olarak saptanabilmektedir (46). Diğer bir izotermal nükleik asit amplifikasyon teknolojisini kullanan moleküler hızlı tanı testi olan Abbott ID Now COVID-19 testi ile yalnızca 5 dakikada sonuç alınabilmektedir. Bu test hastane, klinik, muayenehane ya da salgın merkezleri gibi herhangi bir lokalizasyonda kullanılabilmektedir. Küçük bir tost makinesi büyüklüğünde taşınabilen bir sistem olan bu test ile RdRp geni boğaz, nazal, nazofarengeal ve orofarengeal örneklerde saptanmaktadır. Bu tekniği kullanan testler tek bir ısıda çalışır ve özel laboratuvar ekipmanlarına ihtiyaç duymadan PCR testlerine eşdeğer bir analitik duyarlılık sağlar (47).

4. Serolojik testler

Bu başlık altında hızlı antijen testleri ve antikor testleri değerlendirilmektedir. Hızlı antijen testleri teorikte hızlı sonuç verme ve düşük maliyet gibi avantajlara sahip olmakla birlikte, duyarlılık sorunu nedeniyle güven sorunu göstermektedir. SARS CoV-2 için lateral akım, antijen saptama geliştirme aşamasında olan bir hasta başı test yaklaşımıdır. Bir ticari lateral akım testinde kağıt benzeri bir membran şerit üzerinde iki ince şerit bulunmaktadır. Bunlardan biri altın nanopartikül-antikor konjugat, diğeri ise yakalayıcı antikorlar ile kaplanmıştır. Hasta örneği membran üzerindeki bölgeye aktarıldıktan sonra kapiller akımla hareket eder. Eğer örnekte spesifik antijen varsa ilk şerit üzerindeki konjugat antikor ile bağlanır ve membran üzerinde birlikte hareket ederler, ardından bu kompleks ikinci şerit üzerindeki yakalayıcı antikor tarafından tutulur ve renkli sonuç bandı oluşur. Bu testlerin duyarlılık ve özgüllüğü IgM için %57 ve %69, IgG için %81 ve %100 olarak değerlendirilmiştir (48).

SARS CoV-2 için monoklonal antikorlar henüz hazırlık aşamasındadır. Bu yöntemlerin tanıda kullanılabilmesi için antijeni konsantre edebilecek ya da saptama fazını arttıracak yeni yaklaşımlara ihtiyaç vardır. Viral titrelerin en yüksek olduğu dönemlerde örnek alınması ile de hızlı antijen testlerinin tanısal duyarlılığında iyileşme sağlanabileceği düşünülmektedir (49, 50).

Serolojik testler hali hazırda klinik araştırmalarda güvenilirliği kanıtlanmış ticari reaktiflerin yetersizliğinden dolayı insan koronoviruslarının rutin tanısında yer almamaktadır. Diğer yandan bu testlerin yeni ortaya çıkan koronovirusların epidemiyolojisini anlamamız açısından büyük önemi vardır (51, 52).

Enfekte hastalarda antikor cevabı konağa bağlıdır ve zaman alabilir. Serolojik testler ile IgM, IgA, IgG ya da total antikorlar (tipik olarak kan örneklerinde) gösterilmektedir. Hastaların çoğunda antikor cevabının virusla karşılaşma sonrası 7-11. günlerde geliştiği gösterilmekle birlikte bu süre daha da uzun olabilmektedir. Bu nedenle akut enfeksiyon tanısında antikor testleri faydalı olamamaktadır. Ayrıca iyileşen hastalarda gelişen immünitenin süresi ve sonraki enfeksiyonlara karşı koruyuculuğu da bilinmemektedir. Antikor testleri;

1. Temaslı izlenmesi durumunda (ki RNA saptayan testlerde bu durumda kullanılmaktadır),
2. Lokal, bölgesel, ulusal düzeyde surveyans amacıyla,
3. Virusla karşılaşmış ve eğer koruyucu immünite varsa bağışıklığın gösterilmesi amacıyla kullanılmaktadır.

Koruyucu immünitenin var olduğu düşünülürse serolojik bilgiler, özellikle sağlık çalışanları gibi etkenle tekrar karşılaşma olasılığı yüksek olan meslek gruplarında işe dönüş kararının verilmesinde önemli rol oynayacaktır. Serolojik testler aynı zamanda vaka ölüm oranının belirlenmesi gibi istatistiksel araştırmalarda, yeni geliştirilen PZR testlerinin duyarlılığının belirlenmesinde ve PZR negatif şüpheli hastaların tanısında kullanılabilir (31).

Tanısal olarak antikor dinamikleri ile ilgili şu anki bilgilerimizin çoğu SARS-CoV ile yapılan daha önceki çalışmalara dayanmaktadır. Dolayısı ile antikor üretim sürecinin de benzer olacağı varsayılmaktadır (53).

SARS CoV salgını döneminde IFA, ELISA, Western Blot yöntemlerini içeren farklı serolojik testler geliştirilmiştir. IFA testinde virusla enfekte edilmiş Afrikan yeşil maymun böbrek hücreleri, ELISA yönteminde ise enfekte hücrelerin ekstrakt ya da süpernatantları kullanılmıştır. Her iki yöntem esaslı testler yüksek duyarlılık (%85-100) göstermekle birlikte özgüllükleri düşük kalmıştır. Diğer CoV enfeksiyonlarına bağlı çapraz reaksiyonlar ve otoantikorlar nedeni ile yalancı pozitif sonuçlar gözlenmiştir (54). Sonrasında geliştirilen rekombinant antijenler ile yöntem standardizasyonları sağlanmıştır (55). Virusun N proteininin tam sekans analizine göre SARS CoV N proteini alfa koronavirüsler ile %25-29, beta koronoviruslar ile %33-47 benzerlik göstermektedir. Bu oranlar S proteini için sırasıyla %23-25 ve %29 olarak belirlenmiştir (56).

Walls ve ark. (56), SARS CoV tarafından türetilmiş poliklonal antikorların SARS CoV-2'nin hücre içine girişini önleyerek nötralizasyon oluşturduğunu göstermişlerdir. SARS CoV ve SARS CoV-2 S domainleri %75 aminoasit dizisi paylaşımlarından dolayı, SARS CoV antikorlarının yeni ortaya çıkan SARS CoV-2 virusu üzerine olan etkilerinin değerlendirilmesinin faydalı olacağı düşünülmektedir.

Okba ve ark.(57) RdRP, N ve S1 antijenlerini farklı in-house ve ticari testleri kullanarak değerlendirmişlerdir. Spike protein antijenleri arasında S1, SARS CoV-2 antikorlarını saptamada S' ye göre daha özgül bulunurken, N proteini S1' e göre daha yüksek duyarlılık göstermiştir. Gerçekte serolojik testlerde viral antijenlerle karşılaştırıldıklarında rekombinant proteinler standardizasyon sağlamaları ve daha düşük düzeyde çapraz reaktivite oluşturmaları nedeni ile tercih edilmektedir (57).

Zhao ve ark. (58), doğrulanmış SARS CoV-2 hastalarında serokonversiyonu total (IgA/IgG/IgM), IgM ve IgG antikorları ile sırasıyla %93.1, %82.7 ve %64.7 oranlarında ve 11, 12 ve 14. günlerde saptamışlardır. Diğer bir önemli bulgu olarak nükleik asit testleri ve serolojik testlerin birlikte kullanımının tanısal duyarlılıkta belirgin bir artış oluşturduğunu öne sürmüşlerdir .

Guo ve ark. (59), 82 doğrulanmış ve 58 muhtemel COVID-19 olgusunu (RT-PZR negatif fakat tipik klinik belirtileri olan) erken humoral cevap yönünden ELISA yöntemi ile değerlendirdiklerinde, IgM ve IgA antikor düzeylerinin ikisinde de 8-14. günler arasında artış gösterilirken, IgG düzeyleri 8-14.günlerde artışa başlayıp 15.güne kadar devam etmiş ve 21. günde plato oluşturmuştur. Araştırmacılar aynı zamanda IgM ile nükleik asit testini birlikte çalışıp tek RT-PZR testi ile karşılaştırdıklarında pozitif saptama oranında önemli düzeyde artış olduğunu rapor etmişlerdir.

Luo ve arkadaşları karşılaşma sonrası ve semptomlar başladıktan sonraki dönemlerde serokonversiyonu üç farklı yöntemle (ELISA, lateral akım immünoassay-'LFIA', kemiluminesan immünoassay 'CLIA') araştırmışlar; IgM ve IgG antikorları için ortalama serokonversiyon süresini karşılaşma sonrası 18-20. günler, semptomlar başladıktan sonra ise 10-12.gün olarak göstermişlerdir. Antikor düzeyleri 6.gün sonrası hızla artarken beraberinde viral yükte azalma gözlemişlerdir (60).

SARS CoV-2 antikorlarının tanısal performansını değerlendiren önemli çalışmalar olmakla birlikte, bazı kısıtlamalar da söz konusudur. Örneğin, gerçekte hastanın ne zaman enfekte olduğu ya da örnek alımından ne kadar süre öncesinde semptomatik olduğu ile ilgili belirsizlikler görülmektedir. Bununla birlikte pandemi döneminde gerçek bulaş zamanının saptanmasının zorluğu da göz ardı edilmemelidir (53).

Çalışmalarda dikkat çekici nokta izole IgM antikor pozitifliğinin çok düşük oranda saptanmış olmasıdır. Bu durum düşük antikor düzeylerine ya da antikorun kısa süreli bulunmasına bağlı olabilir. Serolojik testlerin kullanımı ile hastalığın seyri boyunca farklı immünoglobulin izotiplerinin kinetikleri hakkında daha fazla bilgi edinilebilecektir. Ardından antikorların ortaya çıkış zamanları, titreleri ve hastalığın şiddeti gibi klinik özellikler arasında korelasyon olup olmadığı belirlenebilecektir. Bu nedenle kantitatif antikor testlerinin (ELISA, CLIA) kalitatif testlere (kromatografik immünoassay) tercih edilmesi daha faydalı olacaktır. Ayrıca bu konuda çok az bilgi olmakla birlikte, tanı dışında klinisyenlere prognozun değerlendirilmesi açısından da faydalı olabileceği öngörülebilir (53, 61).

Amerika Mikrobiyoloji Topluluğu'nun 23 Mart 2020 tarihli uluslararası COVID-19 toplantı raporunda antikor testlerinin temaslı izlemi, yerel, bölgesel, ülke çapında serolojik sürveyans, virusla enfekte olup bağışıklık kazananları saptamada, tedavi veya profilaksi için kullanılabilecek nötralizan antikorların temin edilmesi için kaynakları belirlemede ve viral RNA testi negatif şüphelilerde tanı amacıyla kullanılabileceği ifade edilmiştir (31).

COVID-19 etkeninin global yayılımının önüne geçebilecek en önemli uygulama virusla enfekte kişilerin doğru tanısının erken dönemde yapılmasına dayanmaktadır. Bununla birlikte RT-PZR temelli testler hala bazı enfekte olguları kaçırabilmektedir. Ayrıca bu testlerin özel alt yapısı olan laboratuvarlarda uygulanması gereklidir. Hızlı ve otomatize testler RT-PZR testinin yanı sıra tamamlayıcı yöntemler olarak kullanılabilir (62). Ancak öncesinde bu testlerin klinik performansları ciddi olarak değerlendirilmelidir. Bu durumda bir an önce referans çalışmalar ve rehberler oluşturarak, devam eden bilimsel ve politik çatışmaların önüne geçilmesi hedef olmalıdır. Ayrıca toplum taraması, epidemiyolojik çalışmalar ve yeni salgınların izolasyonu için de kitlerin güvenilirlik kriterlerinin (duyarlılık, özgüllük, doğruluk, kesinlik) göz ardı edilmeden, örneğin; CE (*Conformite Europeenne*) sertifikasyonu gibi kalite şartlarının oluşturulması gereklidir.

SONUÇ

Aralık 2019 tarihinden bu yana hem ülkemiz hem de dünya gündemini yoğun bir şekilde meşgul eden ve ne kadar süreyle meşgul edeceği de bilinmeyen SARS-CoV-2'nin tedavisi ve aşı çalışmaları için viral genomun ve replikasyon aşamalarının tam olarak anlaşılması önem arz etmektedir. Yine tedavi sürecinde önemli bir belirteç olan mikrobiyolojik tanı yöntemlerinin duyarlılık ve özgüllüklerinin net olarak belirlenmesi ve hastalığın farklı evrelerinde farklı mikrobiyolojik tanı yöntemlerinin kullanılmasıyla ilgili çok sayıda çalışmaya ihtiyaç vardır.

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Radiology of COVID-19 in Children

Çocuklarda COVID-19 Radyolojisi

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ABSTRACT

The coronavirus disease 2019 (COVID-19), which has been accepted as a pandemic since March 2020, has caused millions of patients and hundreds of thousands of deaths all over the world. The diagnosis of which is important due to its high contagiousness, there are many publications evaluating the radiological approach of this disease in adults, however there are very few reports of pediatric patients worldwide. The aim of this study is to evaluate the radiological approach in pediatric COVID-19 patients by literature review and to guide diagnosis and treatment follow-up with radiological findings.

Key Words: Computerized tomography, COVID-19, Pediatrics, Radiology, X-ray

ÖZ

Mart 2020'den itibaren pandemi olarak kabul edilmiş olan Koronavirüs Hastalığı-2019 (COVID-19) tüm dünyada milyonlarca hastaya, yüzbinlerce ölüme neden olmuştur. Yüksek bulaştırıcılığı nedeniyle tanısının önem kazandığı bu hastalığın erişkin hastalardaki radyolojik yaklaşımını değerlendiren birçok yayın yapılmıştır. Ancak tüm dünyada çocuk hastalara ait bildirimler oldukça azdır. Çocuk COVID-19 hastalarında radyolojik yaklaşımın literatür taraması ile değerlendirilmesi, radyolojik bulgular eşliğinde tanıya ve tedavi takibine yol gösterici olması amaçlanmıştır.

Anahtar Kelimeler: Bilgisayarlı tomografi, COVID-19, Çocuk, Radyoloji, Direk grafi

INTRODUCTION

The coronavirus disease 2019 (COVID-19) spread rapidly worldwide starting from China in December 2019 and was declared a pandemic by World Health Organization on 11 March 2020 (1). This single-stranded RNA virus is known to primarily attach to the upper respiratory tract, causing pneumonia. Due to its high and easy contagiousness, its differential diagnosis becomes important especially in this season, when all other viral upper respiratory tract infections increase (2,3).

Even though it is seen as pleasing that the rate of infection of pediatric patients at first was quite low, it is observed that as the number of cases infected by the virus increases, the number of pediatric patients increases. Although the clinics of pediatric patients are milder than adults, they are effective in the spread of the disease. They usually snatch the virus from their families, however the duration of virus spread with their gaita is longer than their family members, therefore they remain infectious for a long time (4). In addition, it is known that, with delayed diagnosis and treatment, the disease can progress and develop lung damage (5). For these reasons, the diagnosis of the disease has become more important in this age group.

Currently, the definitive diagnostic method is the molecular representation of the virus in the body. The definite widely accepted diagnostic method is to show the virus with Reverse Transcription-Polymerase Chain Reaction (RT-PCR) in the

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sample taken with nasal – oropharyngeal swab (6). However, the specificity of this viral nucleic acid test is high and its sensitivity is low (7). Radiological imaging methods come to the fore in cases where the PCR test is unavailable or if the test is a false negativity (3). In addition, the need for imaging methods has increased in the follow-up.

Chest X-ray (CXR) is accepted as the first step imaging method in many upper or lower respiratory tract diseases worldwide. However, it has been reported in many publications that its diagnostic value is quite low in COVID-19 pneumonia (8). It becomes important in the clinical follow-up of diagnosed cases, especially in the group of patients with acute respiratory distress syndrome (ARDS), who need intensive care.

In this pandemic process, thorax computerized tomography (CT) examination is accepted as the most popular radiological examination in showing pneumonic infiltration. Although it is not easy to access all over the world, CT guides the definition of COVID-19 suspicious cases, by showing the infiltration even before the PCR test is concluded. Therefore, early isolation of these patients can contribute to reducing the transmission rate (8).

Case or serial reports of pediatric patients are very low compared to adults. The purpose of this literature review is to evaluate the radiological approach in pediatric patients, to contribute to the diagnosis process in the presence of radiological imaging findings, to evaluate the place of radiology in follow-up during treatment.

IMAGING RECOMMENDATIONS

Many factors should be considered before deciding on imaging methods in COVID-19. First, the radiology department faces the risk of transmission due to the high contagiousness of the disease. Secondly, the examination and the environmental cleaning after the examination requires cost. The third is the radiation which the patient will be exposed (9,10). Radiation becomes more important especially in the child age group.

The clinic of the patient is the most important factor to be taken into consideration in the choice of radiological examination. Thorax radiological imaging findings of COVID-19 disease are similar to many other viral pneumonias and inflammatory diseases (2). Therefore, there should be high clinical suspicion and supported with radiological findings.

CT is not recommended as the first diagnostic examination for pediatric patients. Pediatrics whose clinic is mild, for example, whose symptoms are only fever or coug, should be tested first with PCR. If the test is positive, CT can be performed in case of deterioration in the clinic or inadequate clinical recovery or for differential diagnosis in the presence of underlying diseases such as malignancy, immunodeficiency, diabetes mellitus, heart disease. In children with moderate or severe clinic, the first diagnostic test should be PCR, but CXR must be performed. CT can be used in clinical follow-up to show the degree of pulmonary involvement. It can be use to make other differential diagnoses in the case of PCR negativity or if the disease suspicion continues on CT images, leads to test repetition (11). However, considering the harmful effects of radiation, it is more convinient to prefer CXR in follow-up imaging rather than CT (12).

CHEST RADIOGRAPHY

In a few studies comparing CXR with CT in adults, it is stated that the sensitivity of CT, which is around 90%, is around 30-40% in CXR. It was emphasized that CXR was more effective in the follow-up of the progression than the diagnosis of the disease (13,14). In a series of few patients in pediatrics, CXR has been reported to detect findings in 40% of patients, which is similar to adults (11,15,16).

Whether PCR test result is negative or positive, the normal CXR does not prove that there is no lung involvement. The finding that may indicate COVID-19 in CXR is bilateral, peripheral radiopacity, especially located in the lower lobes (Figure 1). Unilateral, multifocal, lobar, centrally located or diffuse opacities, peribronchial thickening, plevral effusion can be observed as atypical findings (11) (Figure 2). Since these findings can be observed in many other viral or atypical pneumonia, detailed evaluation with CT is required.

COMPUTERIZED TOMOGRAPHY

The most common CT finding in adult patients is bilaterally, peripheral and subpleural, multifocal ground glass opacity (GGO), especially located in the lower lobes. This may or may not accompany consolidation. While centrilobular distribution, pleural effusion and lymphadenopathy are more common in other pneumonias; air bronchogram, reversed halo sign and excessive lobe involvement should suggest COVID-19 (2). As the disease progresses, it has been shown that GGO intensifies, multiple consolidations, fibrotic bands can develop, pleural thickening or bronchiectasis may occur. In the most advanced state, infiltration covers the entire parenchyma and “white lung” may occur. When ARDS develops, it has been shown that patients need for intensive care unit (ICU) and this is the highest cause of mortality (17). Regression of parenchymal involvement observed as signs of healing begins to appear approximately 2 weeks after the onset of the disease.

CT Findings in Pediatrics

Table I: CT differences between adults and pediatrics.

	Adults	Pediatrics
CT findings	more severe	milder
Positive CT	more	less
Numbers of involved lobes	more	less
Ground-glass opacity	wider	focal
Bronchial wall thickening	less	more
Peribronchial distribution	less	more

CT: *Computerized tomography.*

Table II: CT imaging findings of PCR (+) pediatric patients.

	Numberof patients	Normal	Unilateral involvement	Bilateral involvement	CT findings
Lu X et al. (24)*	138	27			• GGO (56/138) • Local patchy shadowing (32 /138) • Bilateral patchy shadowing (21/138) • Interstitial abnormalities (2/138)
Ma YL et al. (25)	115	27			• GGO + consolidation (47/115) • white lung (2/115) • Increased bronchovascular shadows (39/115)
Qiu H et al. (23)	36	17			• GGO (19/36)
Wang XF et al. (26)	34		-	34	• multiple patchy or nodular GGO and/or infiltrating shadows (34/34)
Wang D et al. (27)	31	17			• patchy GGO and nodules, (9/31) • GGO +consolidation (1/31) • Increased bronchovascular shadows (2/31)
Zheng F et al. (28)	24	8	5	11	• bilateral patchy shadows or lung consolidations (24/24)
Xia W et al. (21)	20	4	6	10	• Consolidation with surrounding halo sign (10/20) • GGO (12/20) • fine mesh shadow (4/20) • tiny nodules (3/20) • Subpleural lesions with localized inflammatory infiltration (20/20)
Feng K et al.(29)	15	6			• small nodular GGO (7/15) • speckled GGO (2/15)
Chen A et al. (20)	14	7	3	4	• GGO (3/7) • GGO with consolidation (1/7) • Nodules (1/7) • Bronchial wall thickening (2/7)
Zhong Z. (30)	9	4			• GGO or spot-like mixed consolidation (5/9)
Zhou Y. (31)	9	1			• GGO (1/9) • GGO + consolidation (6/9) • Consolidation (1/9)
Sun D et al. (5)	8		2	6	• multiple patch-like shadows (7/8) • GGO (6/8) • pleural effusion (1/8) • 'white lung-like' change (1/8)
Hu Z et al. (32)	7	7			
Li W et al. (19)	5	2	3	-	• Patchy GGO (3/5)
Liu W. (8)	5	1	-	4	• Patchy GGO (1/5) • Patchy shadows (3/5)
Liu M et al .(33)	5	1	3	1	• Unilat GGO and/ or consolidation (3/5) • bilat GGO (1/5)
Liu H et al. (22)	4	1	2	1	• GGO (1/4) • consolidation (2/4) • air broncogram (1/4) • pleural effusion (1/4)
Lou XX et al. (34)	3				• GGO (1/3) • GGO+consolidation (1/3) • Consolidation (1/3)
Zhang T et al. (35)	3	1			• GGO (2/3)
Rahimzadeh G et al. .(36)†	3	1	-	2	• GGO with consolidation 2/3

Li Y et al (7)	2		-	2	• tiny nodules (1/2) • ncreased and slightly disordered bronchovascular bundles (1/2)
Park JY et al. (37)	1		1	-	• GGO + consolidation (1/1)
Tang A et al. (38)	1	1			
Lin J et al. (39)	1	1			
Pan X et al. (40)	1	1			
Yin X et al. (41)	1		1	-	• Cord shadow (1/1)
Other Case reports (6) ‡	17	4			• GGO (4/17) • GGO + consolidation (6/17) • consolidation (1/17) • Increased bronchovascular shadows, scattered small strip-like opacities (2/17)
Total	512	139	26	75	

CT: *Computerized tomography,* ***GGO:*** *Ground-glass opacity,* ****** *Since 33 of 171 patients in the series had no CT findings, 138 CTs were evaluated* ***†*** *Since 3 of 9 patients in the series had positive PCR result, 3 CTs were evaluated, ‡ taken from Duan et al. (12, 42-52)*

While CT findings are found in 86% of adult patients, this rate has been reported to be 63% in a limited number of pediatric patients (18). COVID-19 has a wide range of non-specific findings in children. The findings are milder than adults, and typical CT findings are less common in children compared to adults (Table I) (16). The most common finding is focal GGO, which is observed in the peripheral and posterior lobes (6, 19) (Figure 3). Compared to adults, GGO is more focal and tends to hold few lobes. It was stated that peribronchial spreading and bronchial wall thickness were observed more in children. Consolidation or interlobular septal thickening can be visualized, although not common (Figure 4.). However, it should not be forgotten that this appearance is also observed in many other atypical pneumonia (20). It can be said that differential diagnosis is difficult in children, it is even more difficult, especially in children with the underlying disease. For example, many other factors such as mycoplasma, RSV, H1N1 can be detected in the immunsupressed malignant patients. It should also be noted that CT findings can also be quite complicated in the presence of coinfection. Clinic and presence of contact history will be the main guide in differential diagnosis (21, 22). For example, while children are more symptomatic in H1N1 and SARS infections, they are more likely to be asymptomatic in COVID-19 (23). The presence of pleural-based distribution, pleural effusion, and lymphadenopathy should suggest other causative viral or atypical pneumonias (11) (Figure 5).

In Table II, we summarized the CT findings of PCR positive COVID-19 cases under the age of 18, which have been reported so far in the literature (5-8,12,19-52). Accordingly, 139 (27%) of 512 CTs were normal, while 373 (73%) had findings. No information was given about unilateral or bilateral findings in 411. In the remaining 101 CT, 26 (26%) of the findings were unilateral, while 75 (74%) were bilateral. While GGO was the most common CT finding (34%), consolidation alone (27%) or consolidation with GGO (18%) were other frequently observed findings. It was observed that pleural effusion, fibrous bands, and reticular pattern were not frequent, but also “white lung” was observed in several patients with severe condition. However, the terminologies used to describe CT findings are not standard. For example, “patchy shadows” was probably used to describe consolidation. The definition of GGO and / or consolidation is not clear enough, so it is not known how many patients have consolidation. Therefore, the rates we give for CT findings should be approximated.

“Halo sign”, followed by Xia et al. (21) in 50 % of patients, is a focal consolidation area with a lower density, accompanied by peripheral GGO. Although it was emphasized that it can be evaluated as a typical finding in pediatric patients, it is not a defined finding in many other CTs in the literature.

In a study in which the CT findings were evaluated by different age groups, bilateral lung involvement was most frequently observed in children under 3 years of age, and unilateral involvement and normal CT findings were higher in children over 6 years of age. Since the immune systems may not be fully mature yet, it has been emphasized that special attention should be paid to children under 3 years old (28).

Although it is not recommended to perform patient follow-up with CT in clinically mild patients, many pediatric patients with nonspecific clinical findings require CT examinations and repetitive PCR tests (29). It was observed that as the disease progressed, GGOs intensified, consolidations were developed at a higher rate, parenchymal involvement became widespread, followed in more lobes, fibrosis, bronchiectasis, air bronchogram, interlobular septal thickening could develop. It was observed that plavral effusion or pleural thickening may be accompanied by “white lung”, which is defined as the most advanced ARDS finding (5) (Figure 6). As expected during the recovery period, the density and number of lesions and the rate of involvement decrease or disappear. Fibrotic bands can remain. (21).

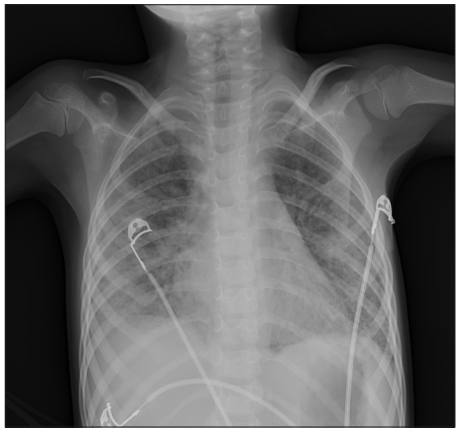

Figure 1: 8 years old, PCR (+) male patient, diffuse radioopacity in both lungs, especially in the lower lobes.

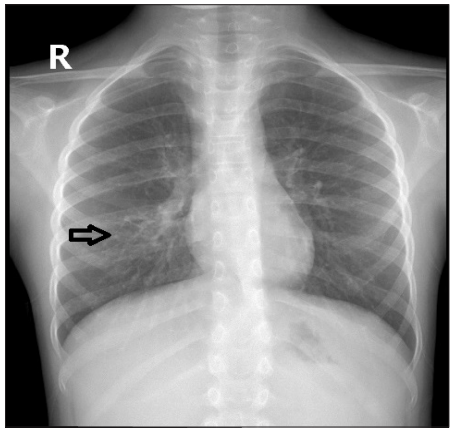

Figure 2: 7 years old, PCR (+) female patient, scattered radioopacity, peribronchial thickening in the right lung lower lobe (open arrow).

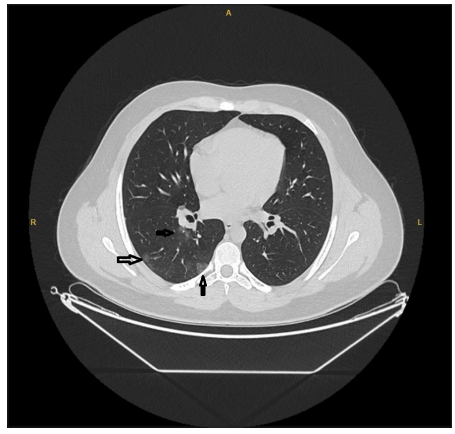

Figure 3: 17 years old, PCR (+) male patient, scattered, focal, peripheral ground glass densities in the right lung lower lobe(arrows).

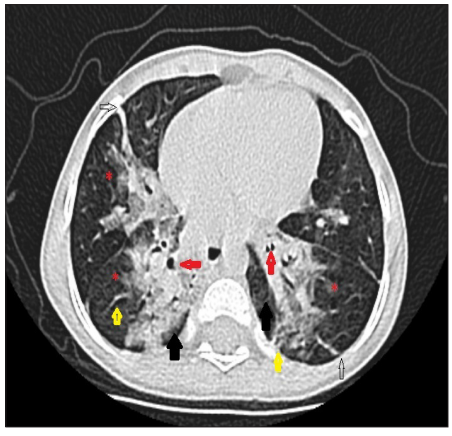

Figure 4: 2 years old, PCR (+) female patient, widespread consolidation (black arrows), air bronchogram (red arrows), ground glass opacity (red stars), interseptal thickening (yellow arrows), fibrotic bands (arrows), mainly observed in the lower lobes in both lungs.

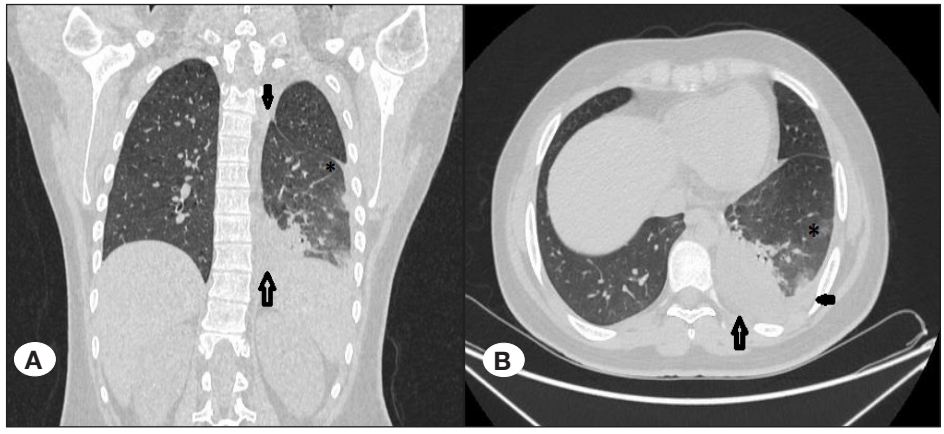

Figure 5: In the coronal **(A)** and axial **(B)** image, pleural-based consolidation in the left lower lobe(arrows), accompanying ground glass opacity (stars) and pleural effusion (little arrows) (3 times COVID-19 PCR test were (-), RSV pneumonia detected).

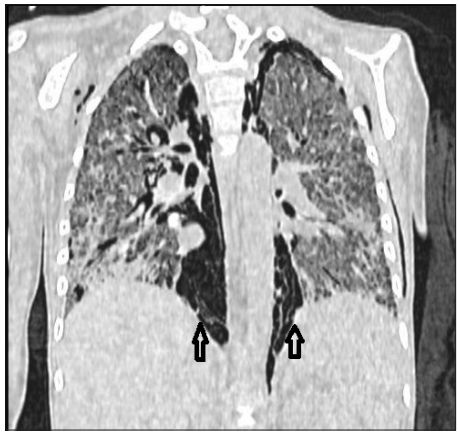

Figure 6: 7 years old, PCR (+) male patient, 'white lung', perimediastinal pneumotorax and pleural fibrotic bands (arrows).

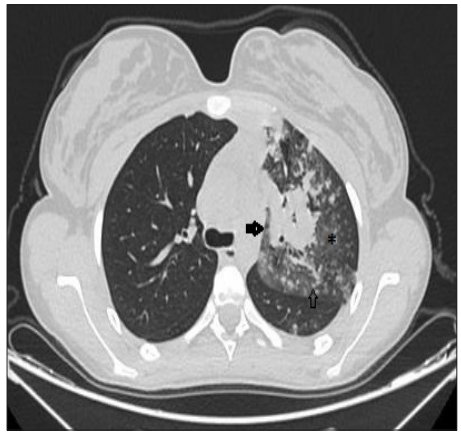

Figure 7: 13 years old, 3 times PCR (-) female patient, consolidation (arrow), ground glass opacities (star), tree-in bud (little arrow) in the upper left lobe.

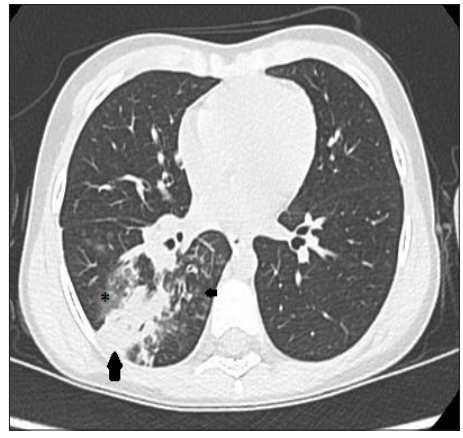

Figure 8: 7 years old, PCR (+) female patient, consolidation (arrow), ground glass opacities (star), tree-in bud (little arrow) in the lower right lobe.

Correlation Between CT and PCR Test

There is no study comparing CT findings with PCR test in pediatric patients yet. In studies comparing the PCR test and CT findings in adult patients, the results of both were generally shown to be compatible with each other (17). However, typical CT findings can be observed in asymptomatic patients with positive PCR test. It is also known that there are patients with typical CT findings, while the PCR test was initially negative,next PCR test may become positive or remain negative (44,53). There were PCR positive patients with normal baseline CT findings, and those with improved infiltration in control CT examinations were also reported. CT findings are mostly observed approximately 10 days after the onset of the disease (54,55). So it is important when CT is applied. Considering the study that reported the sensitivity of the PCR test was 71 % and the sensitivity of CT was 98 %, the value of CT increases especially in the presence of clinical suspicion and contact history (56). Even if the PCR test is negative, it is recommended to repeat the test in the presence of high clinical suspicion and typical CT findings, and the final diagnosis should be made by PCR test result (17) (Figure 7,8).

CONCLUSION

It is very pleasing that the number of children COVID-19 patients are lower than the adults and the clinic is better. Since they are more likely to have the disease asymptomatically, they play an important role especially in the spread of the disease (57,58). Therefore, their diagnosis should be made as soon as possible. Molecular diagnostic methods should be the first step in diagnosis. CXR should be the first choice in patients with mild clinical status. CT should be preferred in the severe clinic. However, CT findings are similar to many other pneumonias. The clinical findings and contact history of the pediatric patient are the two most important factors to be considered before deciding on a radiological examination.

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COVID-19 Management in Pediatric Emergency Medicine

Çocuk Acil Servisinde COVID-19 Yönetimi

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ABSTRACT

Emergency departments are on the front line in the management of Covid-19 cases. Emergency department personal need to be equipped with appropriate personal protective equipment and trained in its use. Pre-triage screening is necessary to prevent nosocomial infection. The clinical presentation of Covid-19 ranges from non-specific symptoms to acute respiratory distress syndrome. Personal in triage must maintain a high index of suspicion when evaluating all patients, but especially those with fever, cough, dyspnea, or signs of a respiratory illness. Healthcare workers who perform aerosol processing should be carefully. Even though morbidity and mortality are rare in pediatric population, clinicians should be aware that they may infect more vulnerable populations and social distance should be encouraged.

Key Words: Children, COVID-19, Pediatric Emergency Department

ÖZ

Acil servisler Covid-19 vakalarının yönetiminde ön saflarda yer almaktadır. Acil servis personeli kişisel koruyucu ekipmanlarla donatılmalı ve kullanımı konusunda eğitilmelidir. Hastane enfeksiyonlarının önlenmesi için ön-triaj taramaları gereklidir. Covid-19'un klinik görünümü spesifik olmayan semptomlardan akut solunum sıkıntısı sendromuna kadar değişebilmektedir. Triaj personeli, özellikle ateş, öksürük, nefes darlığı veya solunum yolu hastalığı bulguları olmak üzere tüm hastaları değerlendirirken yüksek şüphe duymalıdır. Aerosol oluşturan işlemler yapan sağlık çalışanları dikkatli olmalıdır. Çocuk popülasyonda morbidite ve mortalite nadir olmakla birlikte, klinisyenler daha savunmasız, hassas popülasyonlara bulaştırabileceklerinin farkında olmalı ve sosyal mesafe teşvik edilmelidir.

Anahtar Kelimeler: Çocuk, COVID-19, Çocuk Acil Servis

INTRODUCTION

The first Covid-19 case in our country was detected on March 11, 2020. Emergency workers carry a huge responsibility in this pandemic. Structural modifications such as triage place, patient waiting area, observation rooms have been arranged in the emergency departments (1). Patient's orientation (home, hospitalization, admission in intensive care unit) is a central aspect of emergency management. Symptoms of Covid-19 such as respiratory symptoms, fever, and cough are like other viral upper respiratory illness. Therefore, case identification should be made for Covid-19 patients. In our country, the patients are evaluated according to the case definition stated in the Covid-19 guide of the T.C. Ministry of Health (2). In the presence of Covid-19, standard, droplet and contact isolation methods should be applied. Hand hygiene, respiratory hygiene and contact prevention measures are the base methods.

RED FLAG!

Protection of emergency department staff from nosocomial infection is critically important!

Triage

Triage is the process of classifying patients according to their emergency status. In pandemic period to improve infection control, a specific early triage area is required, which includes

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Conflict of Interest /Çıkar Çatışması: *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

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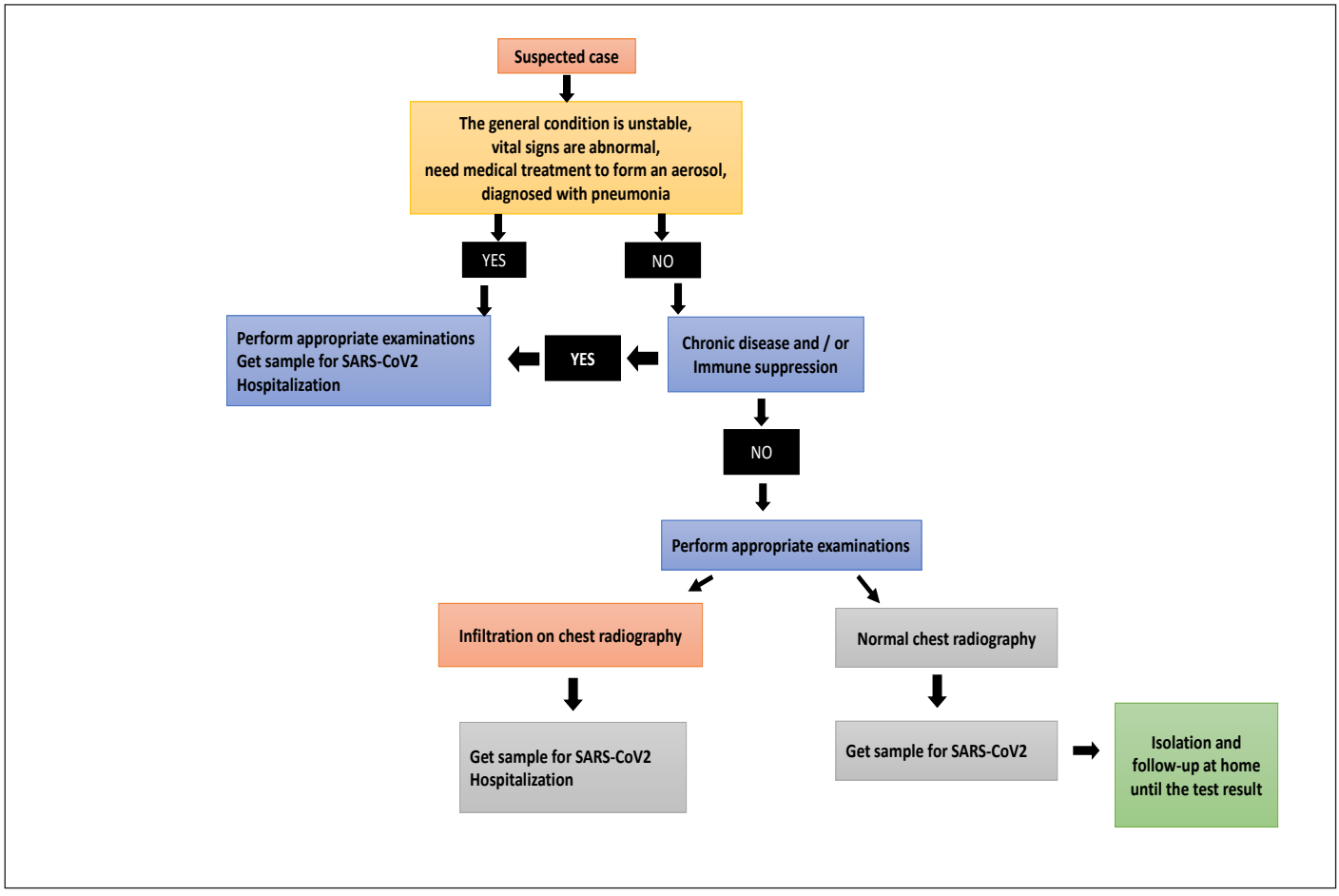

Figure1: Pediatric Covid-19 case management algorithm.

early recognition of the infection status, immediate separation of suspicious cases and appropriate infection prevention measures (3). If possible, this new pre-triage screening should be done before entering the emergency department to prevent nosocomial transmission (4). If there is not enough space, a tent may be built to increase capacity. In this area, a child with a fever, cough, and respiratory distress is recommended to wear a surgical mask. Healthcare workers must be wearing full personal protective equipment (gown, surgical mask, goggles / face shield, gloves) in this area (1).

The primary step of triage in pediatric patients; evaluation of the appearance, respiration, and circulation in a short time by using visual and auditory cues with "Pediatric Assessment Triangle". Today, there is no ideal triage system with high reliability and selectivity in children. Evaluation of vital signs during triage is practically not used frequently. According to our knowledge temperature measurement is included in The Emergency Severity Index. Fever is the most important finding in Covid-19. Therefore, at least fever must be measured in triage area.

Infection protection in emergency room

In the emergency room, normally everyone should use a mask. However, a surgical mask is not enough for aerosol processing such as aspiration, tracheal intubation, tracheostomy, noninvasive ventilation, chest compression and bag-mask ventilation. Healthcare workers who perform such procedures should use masks (N95, FFP2 etc.) that are fully exposed to the face (5).

The administration of cardiopulmonary resuscitation involves performing numerous aerosol procedures and require providers to work near one another and the patient. Emergency airway and tracheal intubation of a child diagnosed with Covid-19 is a high-risk procedure for infection transmission (6). Therefore, operations should be done in a negative pressure room if possible. Patients should be intubated according to the rapid sequential intubation protocol. Intubation should be done by the most experienced person, with one attempt and, if possible, with video laryngoscope in intubation box. Cuffed endotracheal tube should be preferred. Clamp can be attached to the tube before the procedure. If it is necessary to make a bag-mask ventilation during intubation, it should be using with filter and tight seal (5, 6). If high flow nasal cannula treatment is going to be done, the mask is put on the patient after the nasal cannula is placed. Inhaler drugs should be given by aero-chamber or metered dose inhaler (Puff), not by nebulizer. Simulations are highly recommended (3,7).

Laboratory test

Respiratory samples are taken in patients who meet the Covid-19 suspected case definition. Haemogram and C-reactive protein tests are sufficient in patients whose general condition is stable and will be followed up on an outpatient. Additional examinations such as urea, creatinine, sodium, potassium, chloride, aspartate aminotransferase, alanine aminotransferase, total bilirubin, lactate dehydrogenase, creatine phosphokinase, D-dimer and troponin are taken in patients who need hospitalization (7).

Imaging

A chest radiography is taken for each patient with suspected Covid-19. In patients whose respiratory system findings cannot be explained by chest radiography or worsening in the clinic, thorax computerized tomography is performed if necessary. Lung ultrasound findings depend on the stage and severity of the disease (8).

Algorithm of suspected cases

Algorithms should be used for case definitions and appropriate approach. In our country, "Pediatric Covid-19 case management algorithms" are widely used in pediatric emergency departments (Figure 1) (9).

Suggestions on discharge

The patient should be trained on respiratory hygiene. After explaining to the patient and family what to do during the follow-up at home and their criminal liability, a consent form containing this information is signed. All residents should follow their own health status and be told to apply to the health institution when any symptoms appear.

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Coagulation System Abnormalities in Patients With COVID-19 Infection

COVID-19 Enfeksiyonu Olan Hastalarda Koagülasyon Sistemi Bozuklukları

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ABSTRACT

COVID-19 infection caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) in China led to a pandemic all over the world. Although mortality rate between 4.3% to 14.6%, studies have shown that coagulation dysfunction is a major cause of death in patients with severe COVID-19 infection. The majority of the severely ill patients have underlying disease (i.e. diabetes, cardiovascular disease, hypertension) and initially present with respiratory insufficiency but some of them progress to systemic disease causing multiple organ dysfunction. This manuscript reviews coagulation system abnormalities in patients with COVID-19 infection.

Key Words: COVID-19, Disseminated Intravascular Coagulation, Sepsis

ÖZ

Çin'de Şiddetli Akut Solunum Yetmezliği Sendromu-Coronavirus-2'nin (SARS-CoV-2) neden olduğu COVID-19 enfeksiyonu tüm dünya çapında bir pandemiye yol açmıştır. Ölüm oranı %4.3-14.6 arasında değişmekle birlikte, çalışmalar koagülasyon disfonksiyonunun ağır COVID-19 enfeksiyonu olan hastalarda önemli bir ölüm nedeni olduğunu ortaya koymuştur. Ağır hastaların çoğunda altta yatan bir hastalık (diyabet, kardiyovasküler hastalık, hipertansiyon) vardır ve başlangıçta solunum yetmezliği ortaya çıkar, ancak bazıları çoklu organ disfonksiyonuna neden olan sistemik hastalığa ilerler. Bu yazıda COVID-19 enfeksiyonu olan hastalardaki koagülasyon sistemi bozuklukları tartışılmaktadır.

Anahtar Kelimeler: COVID-19, Dissemine intravasküler koagülasyon,Sepsis

INTRODUCTION

COVID-19 infection caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) was first described in December 2019 in Wuhan, China (1). After that, the disease has become a worldwide threat with estimated mortality rates ranging from 4.3% to 14.6% (1,2). Although the mortality is predominantly related to the acute respiratory distress syndrome, COVID-19 associated coagulopathy was also reported in several studies (3-5). Because of SARS-CoV-2 has been detected in various cells in the body, high number of proinflammatory cytokines to be released, promoting a systemic inflammatory response syndrome (SIRS), accelerating cell death in the lungs, liver, heart, kidneys and the adrenal parenchymal organs, which can ultimately lead to multiple organ dysfunction syndrome (MODS) (6). As inflammatory reactions occur in the all organs of the body, the microvascular system is damaged, leading to abnormal activation of the coagulation system, which pathologically manifests as generalized small vessel vasculitis and extensive microthrombosis (3-5). This manuscript reviews coagulation abnormalities in patients with COVID-19 infection.

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Contribution of the Authors / Yazarın Katkısı: GURLEK GOKCEBAY D: Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar, Taking responsibility in the writing of the whole or important parts of the study. ***OZBEK NY:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar,Taking responsibility in the writing of the whole or important parts of the study.

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Inflammation and Coagulation

SARS-CoV-2 targets respiratory epithelium and it enters host cells through the angiotensin converting enzyme 2 (ACE2) receptor (1,2). This viral invasion initiates complex systemic inflammatory response as a part of innate immunity. Microorganisms and their components bind to the pattern-recognizing receptors on host defense cells inducing proinflammatory cytokines and coagulation. Coagulation is activated by the inflammatory response through several mechanisms. Products of microorganisms, polyphosphates, activates platelets and FXII that triggers the intrinsic coagulation pathway. Activation of complement system also activates coagulation. Additionally, neutrophil extracellular traps (NETs) composed of components of cell-free DNA and histones activate the contact pathway of the coagulation. Finally, the proinflammatory cytokines activate the vascular endothelial cells and as a consequence of prothrombotic effects, endothelial injury occurs (7). These cytokines promote release of ultralarge vonWillebrand factor (vWF) multimers, production of tissue factor (TF) and factor VII (FVII) leading to increased thrombin generation, and decrease levels of endogenous anticoagulants such as tissue factor pathway inhibitor (TFPI), antithrombin, and activated protein C. The interaction between endothelial cells, platelets, macrophages, neutrophils, the complement system and the coagulation system results in a hypercoagulable state with increased levels of procoagulants, decreased levels of anticoagulants, and depressed fibrinolysis. If the activation of coagulation system cannot be taken under control, can lead to sepsis-induced disseminated intravascular coagulation (DIC). Sepsis-induced DIC (SIC) is characterized by an infection and systemic activation of coagulation, which can cause organ dysfunction as a result of interactions between coagulation and inflammation. Coagulation abnormalities associated with SIC are less severe and occur earlier in patients with sepsis than DIC. If the underlying etiology of sepsis is not resolve, the changes continue with SIC progressing to DIC. The International Society of Thrombosis and Haemostasis (ISTH) has developed diagnostic criteria for DIC and SIC score (8).

Initial reports from China during COVID-19 outbreak have disclosed that the severely ill patients had met both DIC and SIC criteria (1,9-11). Chen et al.(1) analyzed the characteristics of the first 99 patients hospitalized in Wuhan, and reported 5% of the patients had an elevated prothrombin time (PT), 6% had elevated activated partial thromboplastin time (aPTT), and 36% had elevated D-dimer. Wang et al. (9) also analyzed 138 patients with COVID-19 infection and reported 38 of them had transferred to the intensive care unit. When non-survivors compared with the survivors, showed higher D-dimer levels (2.12µg/ml vs. 0.61 µg/ml) and progressive lymphopenia (9). Another study included 191 patients has reported to the mortality rate of 28% and elevated D-dimer, PT, interleukin-6, and troponin levels were associated with mortality. Multivariate analysis showed that a D-dimer level higher than 1.0 mcg/mL on admission had predicted mortality (OR 18.42 [CI 2.64-128.55], p=0.003) (10). In the largest analysis of clinical cases in China, which included 1099 patients, it was noted that D-dimer was ≥0.5 mg/L in 46.4% of the patients, and it was higher in those with severe disease compared to non-severe group (11).

Tang et. al (3) analyzed the coagulation parameters of the 183 patients with COVID-19 positivity. Totally, 15 (71.4%) of the 21 patients who did not survive, and 0.6% of the survivors met criteria of DIC according to ISTH with median 4 days after admission. On admission, the non-survivors had significantly higher D-dimer and fibrin degradation product (FDP) levels, and longer PT compared to survivors. By the late hospitalization, non-survivors had findings of progressive DIC with decreased fibrinogen and antithrombin III levels, this suggested that coagulation parameters during the course of the disease significantly associated with prognosis (3). Ranucci et al. (12) noted elevated IL-6 levels on admission in 16 COVID-19 patients with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. They reported that increased interleukin-6 (IL-6) levels correlated with increased fibrinogen levels, demonstrating the link between inflammation and procoagulant changes (12). All of the results of these studies revealed that during the early phase of COVID-19 infection, coagulation abnormalities are seen but do not cause clinical bleeding. As the disease get severe, coagulation abnormalities progress to SIC and then to DIC. Additional factors including medications used and underlying diseases (diabetes, hypertension, and cardiovascular disease) may affect to progress to SIC or DIC. Consequently, coagulation abnormalities occur in COVID-19 infected patients are most likely a result of the excessive inflammatory response (3,13).

A recent post-mortem case series regarding COVID-19 associated lung pathophysiology disclosed that in patients with severe COVID-19 infection, there was diffuse alveolar damage with a mild to moderate mononuclear cell infiltration consisting of CD4+ cell aggregates around thrombosed small vessels, and associated hemorrhage. Another mechanism that may have contributed to death is thrombotic microangiopathy which was restricted to the lungs. This process may involve activation of megakaryocytes, possibly those native to the lung, with platelet aggregation and platelet-rich clot formation, in addition to fibrin deposition. Small vessel thrombus formation in the lung periphery was associated with foci of alveolar hemorrhage in many cases (14). Collectively, all these data suggest that the diffuse pulmonary inflammation observed in COVID-19 is associated with a novel pulmonary-specific vasculopathy which recently termed pulmonary intravascular coagulopathy (PIC) as distinct to DIC. Though the pathophysiology of PIC is scarcely understood, ACE-2 receptor used by SARS-CoV-2 is expressed on both type II pneumocytes and vascular endothelial cells in the lungs, which may suggest the possibility of direct pulmonary endothelial activation and damage (5). A recent report demonstrated viral inclusions within endothelial

cells and sequestered mononuclear and polymorphonuclear cellular infiltration, with evidence of endothelial apoptosis in the lungs (15). In the setting of PIC, it was hypothesized that the refractory ARDS occurred in severe COVID-19 is related to ventilation (V) and perfusion (Q) disequilibrium in the lungs where alveoli and pulmonary microvasculature exist in close anatomical localization (5). Moreover, emerging data showed that severe COVID-19 is also associated with a significant increased risk for developing deep vein thrombosis and pulmonary embolism (16,17).

Management of Coagulopathy

Based on the experience from published literature, serial measurement of PT, PTT, D-dimer, platelet count and fibrinogen can be helpful in determining prognosis in COVID-19 patients requiring hospital admission. Evaluation of endogenous coagulation system with PT and PTT can be used to determine heparin dosage or hypercoaglable state. Prolonged thrombin time (TT) and decreased fibrinogen can suggest hypofibrinogenemia. For the evaluation of fibrinolytic system, D-dimer and FDP are necessary, if they increased indicates the possibility of thrombosis, as deep vein thrombosis, pulmonary embolism, myocardial infarction or cerebral infarction (18,19). If there is worsening of these parameters, more aggressive critical care support is necessary and 'experimental' therapies and blood product support as appropriate should be considered. If these markers are stable or improving together with the patient's clinical condition, it gives a confidence for stepdown of treatment. In case of multi-organ failure in patients with sepsis and coagulopathy, inhibiting thrombin generation may have beneficial in reducing mortality (8). Additionally, ISTH DIC score is recommended to diagnose COVID-19-related coagulation dysfunction, ≥5 points is associated with overt DIC. Unfractionated heparin / low molecular weight heparin (LMWH) are recommended for anticoagulant therapy to severe COVID-19 patients with coagulation dysfunction (17,18). Classic heparin can be preferred for a short half-life, a convenient monitoring process and can be neutralized with protamine (18). LMWH has a longer half-life, a prophylactic dose (4000 U enoxaparin once daily) should be considered in all patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than $25x10^9$ /L; monitoring advised in severe renal impairment; abnormal PT or aPTT is not a contraindication). LMWH is also protect critically ill patients against venous thromboembolism and have anti-inflammatory properties which may be an added benefit in COVID infection (19). Tang et al.(20) reported the benefit of this approach in 449 patients with severe COVID-19; of which 99 (22%) received heparin (94 patients with enoxaparin, and 5 with unfractionated heparin) at prophylactic doses. Although no difference was observed in the 28-day mortality in those received heparin compared to those who did not, but a stratification by SIC score identified lower mortality in patients treated with heparin when SIC score was >4. A similar reduction of mortality was also noted in those with D-dimer > six-fold of upper limit of normal (32.8% vs 52.4%, P=0.017) (20). Fogarty et al. also analyzed whether there were differences in coagulopathic features in 83 COVID-19 infected Caucasian compared to Chinese patients. Unless contraindicated all of the hospitalized patients with COVID-19 received weight- and renal- appropriate doses of LMWH as thromboprophylaxis. D-dimer levels were above the normal range in 67% of the patients, whereas PT and PTT were normal on admission. However, fibrinogen levels were significantly increased probably due to acute phase reactant. During hospitalization period, none of the patients developed systemic DIC, but progressive increase is seen in D-dimer levels in patients transferred to intensive care unit. They concluded prophylactic LMWH does not significantly impact the progressive increase in D-dimer levels observed in patients with severe COVID-19 (5). However, Klok et al. (21) noted a 31% cumulative incidence of thrombosis in a cohort of 184 ICU patients with COVID-19, despite antithrombotic prophylaxis, and the vast majority of them (81%) were pulmonary emboli. Likewise, Corrado et al. analyzed 388 patients (median age 66 years, 16% requiring intensive care) with COVID-19 and despite thromboprophylaxis, thromboembolic events occurred in a cumulative rate of 21%. Half of the events were observed within 24 h of admission. Venous thromboembolism was shown in 16 (36%), pulmonary embolism was shown in 10 (7.7%), ischemic stroke was 2.5% and acute coronary syndrome was 1.1% of the patients (22). Therefore, when pulmonary embolism is suspected, objective diagnosis with radiologic methods should be performed quickly and appropriate heparin doses given to the patient.

Bleeding is unusual during COVID-19 infection, but even if it develops, blood component support according to ISTH guidelines should be given. Critically ill patients at high-risk of mortality may benefit from treatment strategies to inhibit excessive inflammatory responses, but the success of these therapies may depend on the time course and evolution of the infection. Serine protease inhibitors including antithrombin, C1 esterase inhibitor, and protein C are decreased in the setting of the inflammatory response to infection (8). Fibrinolytic shutdown that also occurs in sepsis is characterized by increased plasminogen activator inhibitor-1 (PAI-1) activity resulting in low D-dimers. Vascular endothelial injury causes further thrombocytopenia, reduction of natural anticoagulants, but also hemostatic activation as the phenotypic expression of thrombotic DIC. Analysis of septic patients who are coagulopathic and receive serine protease inhibitors such as antithrombin or thrombomodulin suggest there may be a survival benefit (23). Wang, et al. (24) reported 3 cases of off-label intravenous administration of tissue plasminogen activator (tPA) for patients with COVID-19 with ARDS and respiratory failure. In all 3 cases demonstrated an initial improvement ranging from a 38% to ~100%, but this response was transient and lost over time in all patients after completion of their tPA infusion (24).

Additionally, in severe COVID-19 patients, the antithrombin III activity should be maintained above 80% (18,19). Another recommendation is viscoelastic tests (thromboelastometry) which used to evaluate the dynamic changes in coagulation function of severe COVID-19 patients, if possible (19). In patients with secondary liver failure, plasma exchange can decrease the dosage of vasoactive drugs, remove inflammatory cytokines, reduce capillary leakage and platelet consumption (25).

In conclusion, hyperinflammation and detrimental immunothrombosis may be central to the pathophysiology of COVID-19. Platelet hyper-reactivity, hypercoagulability, hypofibrinolysis, complement overactivation, in the presence of underlying inflammatory-induced endothelial dysfunction likely lead to a state of COVID-19 induced coagulopathy. The recommendation of the Ministry of Health is close monitoring of the coagulation markers in these patients, and enoxaparin should be given 40 mg a day in patients with D-dimer <1000 ng/mL, and 0.5 mg/kg two times a day in patients with severe disease or D-dimer >1000ng/mL (26). Early initiation of thromboprophlaxis in patients infected with COVID-19 can be life-saving for these patients.

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SARS COV-2 Infection in Children with Leukemia

Lösemili Çocuklarda SARS COV-2 Enfeksiyonu

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directed great attention and anxiety all over the world. Epidemiologic models predict that the current COVID-19 pandemic will last several months or even several years, until the development of a vaccine and/or herd immunity. Although the course of the infection is often not severe in children, it can be life threatening especially in immunocompromised children with leukemia. Hematopoietic and lymphoid cancers are accounting for approximately 40% of all childhood cancers. The five-year survival rate for childhood cancer has approached to 70% and more than 80% for leukemia in our country. During COVID pandemic, children with leukemia may also have COVID-19 infection, especially when their bone marrow is depressed due to chemotherapy. It is observed that factors such as the underlying type of cancer, status of remission, or having stem cell transplantation may affect the prognosis. As well as standard and proven treatments for febrile neutropenia, all tests and treatments should be applied very quickly and properly for COVID 19 as is all suspected patients. These efforts may contribute to increase the survival of our children with cancer. Given the absence of data to address concerns related to SARS-CoV-2 infection while on chemotherapy, questions are increasing about the approach for management of systemic immunosuppressive therapies, i.e. ceasing or reducing the immunosuppressive medications in children with leukemia.

The current rapid worldwide spread of COVID-19 necessitates identifying optimal preventive strategies and effective medical management. In this report, we tried to review appropriate literature-based approaches for prevention, diagnosis and management of treatment protocols for children with cancer during the pandemic period.

Key Words: Children, Medical Management, Leukemia, SARS COV-2 Infection

ÖZ

Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) tüm dünyada dikkatle ve kaygıyla izlenmektedir. Epidemiyolojik modeller, mevcut COVID-19 pandemisinin bir aşı ve / veya sürü bağışıklığı gelişene kadar birkaç ay hatta birkaç yıl süreceğini tahmin etmektedir. Çocuklarda COVID-19 enfeksiyonu genellikle hafif seyretmekle birlikte, özellikle bağışıklığı zayıflamış lösemili çocuklarda hayatı tehdit edebilir. Hematopoetik ve lenfoid kanserler tüm çocukluk çağı kanserlerinin yaklaşık %40'ını oluşturmaktadır. Çocukluk çağı kanserlerinde ülkemizde beş yıllık sağkalım oranı %70'e ve lösemi için bu oran %80'e ulaşmıştır. COVID-19 salgını sırasında, lösemili çocuklarda, özellikle kemoterapi nedeniyle kemik iliğinin baskılandığı dönemde, COVID-19 enfeksiyonuna yakalanma riski yüksek olabilir. Altta yatan kanser türü, kanserin remisyon durumu veya kök hücre nakli yapılmış olması gibi faktörler de enfeksiyona cevabı etkileyebilir. Nötropenik ateşli hastalarda, standart ve kanıtlanmış tedavilerin yanı sıra, COVID 19 için şüpheli hastalarda olduğu gibi tüm testler ve tedaviler çok hızlı ve uygun bir şekilde uygulanmalıdır. Bu çabalar kanserli çocuklarımızın hayatta kalma oranını arttırmaya katkıda bulunacaktır. Kemoterapisi devam eden hastalarda SARS-CoV-2 enfeksiyonu ile ilgili verilerin yeterli olmaması nedeniyle, lösemili çocuklar gibi sistemik immünsüpresif tedavileri devam etmesi gereken hastalarda, immünosüpresif tedavinin azaltılması veya ertelenmesi gibi sorulara cevap aranmaktadır.

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COVID-19'un dünya çapında hızla yayılması, hastalıktan korunmak için gerekli stratejilerin ve etkin tıbbi tedavilerin geliştirilmesinii gerektirmektedir. Bu yazıda pandemi döneminde lösemili çocuklarda gelişebilecek COVID-19'un önlenmesi, tanı koyulması ve enfeksiyon geliştiğinde tedavi protokollerine yönelik literature dayalı uygun yaklaşımları derlemeye çalıştık.

Anahtar Kelimeler: Çocuklar, Tıbbi Tedavi, Lösemi, SARS COV-2 Enfeksiyonu

INTRODUCTION

In March 2020, World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) pandemic, which is caused by a new virus, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Thereafter, a rapid increase in the number of patients and deaths due to this disease directed great attention and anxiety all over the world. Since morbidity and mortality of the disease is higher among adults, especially elders, limited reports have analyzed pediatric patients infected with SARS-CoV-2 (2). From the case series, it appears that children have milder clinical symptoms compared to adults, and are less commonly affected by SARS-CoV-2 (3-9). Nevertheless, that could also mean that children might not be tested for SARS-CoV-2 as frequently as adults. Risk factors for the disease have been defined at the beginning of pandemics, particularly among elderly. However, new signs and symptoms such as COVID-eye, and COVID-toe are still including in the diagnostic list (10-12). Fairly or uncontrolled medical conditions, such as chronic lung disease or moderate to severe asthma, serious heart conditions, severe obesity, diabetes, chronic kidney disease undergoing dialysis, and liver disease are among the risk factors for morbidity and mortality (13-14). Besides, immune compromised conditions, including cancer treatment, bone marrow or solid organ transplantation, and congenital or acquired immune deficiencies, have been associated with increased risk of complications from SARS-CoV-2 infection (14-16). Chinese Center for Disease Control and Prevention Report declared the overall case-fatality rate as 2.3% that was higher among those with preexisting comorbid conditions, and 5.6% for patients with cancer (17,18). Epidemiologic models predict that the current COVID-19 pandemic will last several months or even several years, until the development of a vaccine and/or herd immunity (19).

Although the course of the infection is often not severe in children, it can be life threatening especially in immunocompromised children with leukemia. Given the absence of data to address concerns related to SARS-CoV-2 infection while on chemotherapy, questions are increasing about the approach for management of systemic immunosuppressive therapies, i.e. ceasing or reducing the immunosuppressive medications in children with leukemia.

Aim

There are limited pediatric case reports and case series concerning children with leukemia and COVID-19. However, the epidemiological and clinical patterns of the disease in pediatric patients remain uncertain despite the worldwide spread. In this report, we aimed to review on SARS-CoV-2 infection in children with leukemia in order to provide proposals for the prevention and management of COVID-19 in this population.

Children with Leukemia

According to the collaborative report of Turkish Pediatric Hematology Association (TPHD) and Turkish Pediatric Oncology Group Association (TPOG), the five-year survival rate for childhood cancer has approached to 70% and more than 80% for leukemia in our country (20). Hematopoietic and lymphoid cancers are accounting for approximately 40% of all childhood cancers. Cancer patients are vulnerable to certain infections as well as to COVID-19. It is observed that factors such as the underlying type of cancer, status of remission, or having stem cell transplantation may affect the prognosis (21-23).

During COVID pandemic, children with leukemia may also have COVID-19 infection, especially when their bone marrow is depressed due to chemotherapy. As well as standard and proven treatments for febrile neutropenia (broad-spectrum antibiotic, supportive treatments), all tests and treatments should be applied very quickly and properly for COVID 19 as is all suspected patients. These efforts may contribute to increase the survival of our children with cancer.

Individuals affected by cancer are more susceptible to infections due to coexisting chronic diseases, overall poor health status, and systemic immunosuppressive states caused by both cancer and anticancer treatments. Leukemia itself may be developed on the background of an immune deficiency, furthermore cancer treatment may itself result in secondary immune deficiency. Immune system dysfunction in patients with leukemia is mostly related to systemic immunosuppressive therapies rather than the malignancy itself, including impaired humoral antibody responses and cell-mediated immunity, qualitative and quantitative phagocytic defects, and disruption of cytokine release. In addition, malnutrition, antibiotic therapy, impairment of mucosal membrane barriers provide ready access for endogenous microbiological flora and other opportunistic pathogens (24,25).

In practice, patients with leukemia who have an infection are generally classified as neutropenic and non-neutropenic. Degree and duration of neutropenia is the most important and readily available measurement of susceptibility to infection. Neutropenia with a neutrophil count ≤0.5x109/L is a serious risk factor for infection. Profound neutropenia is defined as

an absolute neutrophil count ≤0.1x109/L and prolonged neutropenia is defined as neutropenia lasting >7 days. They are both related to the frequency and severity of the infection. To assess the risk of susceptibility to infection, the status of the primary disease such as remission-induction, remission or relapse, the treatment phase should also be considered. Beyond neutropenia, leukemic children may also have impaired cell-mediated immunity (25). The number and percentage of CD4+ T lymphocytes are used as a measure of susceptibility to opportunistic infections (26). In children with leukemia, chemotherapeutics, irradiation, and malnutrition, usually diminish T-lymphocyte activity. (25).

There are many viruses that can result in infections in pediatric cancer patients. Respiratory viral infections can cause significant morbidity and mortality. Viral infections are typically not life threatening in those who are receiving less intense therapy. However, certain viruses such as Herpesviruses, Cytomegalovirus, and Ebstein Barr virus may cause serious infection and mortality in the most intensively treated children, especially in children with acute myeloid leukemia and those who had hematopoietic stem cell transplant (27).

COVID-19 in Patients with Cancer

After the beginning of COVID-19 pandemic, limited reports released concerning pediatric patients among many publications. Although there are reports stating that children at all ages are susceptible to COVID-19, clinical manifestations has been less severe compared to those in adult patients. Children under the age of three years or children with underlying conditions, such as impaired lung function, immunosuppression or heart disease are the most frequently affected groups (2,3,17).

Studies, including mostly adult patients, have been stated that cancer patients with COVID-19 infection who admitted to the intensive care unit (ICU) were approximately 1-2% in Wuhan, China; 6% in New York City, USA, and 8% in Lombardy, Italy (28-33). A recent report from Italy revealed that 20% of all deaths from COVID-19 were in patients with active cancer (34). A multi-center study, comprising 105 cancer patients and 536 age-matched non-cancer patients (median age 64 years) who were confirmed with COVID-19, revealed that patients with cancer had higher risks in all severe outcomes. Among them, patients with hematological cancer, lung cancer, or metastatic cancer disclosed severe events more frequently compared to those in non-cancer patients. However, non-metastatic cancer patients experienced similar frequencies of severe conditions compared to those observed in patients without cancer. Patients who received surgery for cancer treatment had also higher risks of having severe events, while patients who had only radiotherapy did not demonstrate significant differences in severe events when compared to patients without cancer (22). According to this report, patients who had severe types of cancer or had intensive treatment modalities appear to be more susceptible to COVID-19 complications. A report by Liang et al. (35) included 18 elderly patients (mean age 63 years) with heterogeneous cancer diagnosis. The report revealed that patients who underwent chemotherapy or surgery in the past month had higher risk (39% vs 8%) of clinically severe events (being admitted to the ICU, requiring invasive ventilation, or death) compared to those who did not receive those treatments. A cohort study at two centers in Wuhan revealed that among 128 hospitalized adult patients with hematological cancers, 13 (10%) developed COVID-19. Subjects with hematological cancer and COVID-19 appeared to have more co-infections including bacteria, fungi and other viruses. They reported hospitalized patients with hematological cancers have a similar case rate of COVID-19 compared with normal health care providers, but have more severe disease and a higher case fatality rate, related predominately to bacterial coinfections. Those patients with hematological cancer, who were symptomatic, had significantly decreased hemoglobin, lymphocyte count, lymphocyte subset, and platelet count; and higher concentrations of D-dimer (36).

An analysis of 334 adult patients with cancer from USA accounted 6% of patients diagnosed with COVID-19. Cancer patients under age 50 had a fivefold higher mortality rate than those in this age group without cancer (37). In another report from USA, case fatality rate was found to be 37% for hematologic malignancies, and 25% for solid tumors (38). Boulad et al. (39) conducted a research in 120 asymptomatic pediatric patients with cancer, without known exposure and symptoms. They found that the rate of SARS-CoV-2 positivity was only 2.5% and they observed a 14.7% rate of SARS-CoV-2 positivity in their asymptomatic caregivers. Only one patient with COVID-19 required hospitalization, all other children were managed at home. They suggested that pediatric patients with cancer may not be more vulnerable to SARS-CoV-2. However, unrecognized SARS-CoV-2 infection in asymptomatic caregivers is an important problem for the control of infection. A major survey on SARS-CoV-2 infections in pediatric patients on anti-cancer treatment including patients from 25 countries disclosed that only nine patients were stated positive for COVID-19. Eight of them had asymptomatic to mild disease (40).

Infection Control Measures in Centers Caring for Cancer Patients

In Turkey, Public Health General Directorate of the Ministry of Health, published guidelines for current pandemic for both public and health care professionals (41,42). Furthermore, in recognition of the need to protect health workers and high-risk patients, infection control measures in centers caring for cancer patients were also settled to reduce the exposure of patients and staff member to possible infection with COVID-19.

In addition to the strict measures, in the early period COVID hospitals and COVID care services have been established. According to these guidelines, patients and their relatives should be informed about COVID-19 symptoms and prevention methods. General preventive measures (social distancing, hand washing, limiting the exposure to other people, covering a facemask) are obligatory rules. Patients and their relatives should be questioned for symptoms and signs of COVID-19 prior to admission to outpatient chemotherapy units. If possible, immunosuppressed children should be isolated from other pediatric patients. They should also warn off using public transport and visiting crowded areas.

The outpatient visits of the patients should be reduced as much as possible in order to decrease new infections. Less frequent controls for stable patients could be recommended, and the control of patients who are under follow-up in remission should be postponed according to the decision of attending physician. Radiological examinations should be delayed in this period; especially ultrasonography carries high transmission risk due to contact (43). Health professionals should separate into teams, by working on alternate days or weeks and not sharing offices and common areas, in order to avoid infection or preventative quarantine in the whole staff in the same period (44,45). Clinical and outpatient application, and the attendant should be limited in number. To minimize face-to-face visits, telephone calls or digital platforms could be implemented in practice during the pandemic for visits and screening COVID-19 symptoms or for sustainable new models of cancer care, where available. Telehealth may provide contribution for patients living in remote areas or could be used for meetings with colleagues, particularly multidisciplinary tumor boards, as well as patient consultations.

If possible, each hospitalized patient should be placed in a single negative pressure room. Nebulizers, oxygen masks or nasal continuous positive airway pressure systems should not be used on an open ward (46,47). Aerosol-generating procedures such as intubation and bronchoscopy increase the risk of viral transmission and nosocomial transmission of COVID-19 is one of the important main challenge (48). In order to continue the treatment of cancer patients without interruption and prevent infection transmission, staff (physician, nurse, secretary, cleaning staff) working in chemotherapy and/or radiotherapy departments should not be assigned to other units and the number of working personnel should be limited. The healthcare workers should take standard, contact and droplet isolation measures. The use of gloves, masks, glasses, bones and gowns, is essential for safe care of patients and healthcare workers to reduce risks of transmission on pediatric hematology-oncology units. The personal protection equipment are also recommended during clinical visits. People visiting the patient visit should be limited in number. All the doctors and patients in hematology-oncology units should be tested every week (49). If a patient undergoing chemotherapy and / or radiotherapy is found to be positive for COVID-19, necessary isolation measures should be taken, and the decision to continue, stop or delay in oncological treatment should be made by the oncology physician (45,50).

Treatment in Immunocompromised Patients

The decision to begin and continue cancer treatment during this crisis is challenging given the risk of death from cancer versus death or serious complications from SARS-CoV-2. In patients with suspected COVID-19 infection, it may be recommended to start and continue cancer treatment. However, the decision to start treatment in newly diagnosed patients should be considered after careful evaluation of the goals of the treatment, the general condition of the patient, the ability to tolerate treatment, and the risk of COVID-19 infection (51,52). It is advisable to obtain an informed consent from parents and adolescent patients with leukemia and COVID-19 before treatment (53). Induction treatment for patients with cancer, scheduled chemotherapy should not be delayed or interrupted unless COVID-19 is suspected or diagnosed. In case of leukemia patient tested positive for SARS-CoV-2 infection, immunosuppressive cancer therapy should be postponed. There are no accepted international guidelines and consensus to answer when can cancer treatment be safely restart after the diagnosis of COVID-19. It is recommended for most patients, to stop immunosuppressive therapy until symptoms from COVID-19 have improved. Chemotherapy could be restarted once symptoms were improved and after two sequential negative tests after 24 hours apart obtained. Balancing the risk/benefit ratio should be done in rapidly progressing cancers, and initiation of cancer treatment must be individualized (54-58).

As SARS-CoV-2 has an incubation period of 2–7 days, it can be recommended a treatment delay of no more than 7 days to allow a brief period of observation to screen for COVID-19 in suspected children. Some authors recommend no more than 7-day-delay in the consolidation phase and intermediate phase of chemotherapy and no more than 14 days in the maintenance chemotherapy for patients in the remission phase with acute lymphocytic leukemia and acute non-lymphocytic leukemia. It is also advised to interrupt the treatment in infected patients with leukemia, until two negative results will be obtained (51,57).

In case of patients diagnosed with COVID-19, patients whose disease is in remission, COVID-19 should be treated first. For children who are not in remission, they should be treated for COVID-19, and chemotherapy for the primary disease should be temporarily delayed or reduced according to the patient's situation (54-57). The increase in the maximum delay before chemotherapy strikes a balance between the potential risk of SARS-CoV-2 infection and tumor recurrence.

According to the literature, timing of surgery and/or radiation schedules may be altered, and major surgeries should be

postponed or cancelled (50). International radiation oncology groups recommends for alternative radiation treatment schemes. In case of radiotherapy is required, hypofractionation (ie, by increasing the dose per fraction while reducing the number of daily treatments) should be considered to maintain clinical efficacy and safety (59).

Cancer patients with fever should be tested also for COVID-19, and comprehensive usual evaluation should be performed for alternative causes of fever in patients with febrile neutropenia. During the influenza season, it is reasonable to test for influenza together with SARS-CoV-2 testing. If a patient with leukemia has symptoms that may be related to COVID-19, the treatment for COVID-19 should be started immediately at hospital. In this situation, waiting to obtain the polymerase chain reaction result would be late. Early empirical treatments are very critical for immunocompromised children with fever. Since it is known that immunocompromised patients may have prolonged viral shedding, treatment duration may also be extended (60,61). Supportive care should be provided early to relieve symptoms. To date, no specific and effective antiviral treatment recommended for COVID-19 is available. Potential drugs, which are in clinical use for adults, have not been tested systematically in children, and clinicians are waiting for the results of clinical trials testing the efficacy of these drugs in children.

Blood Products

There may also be problems with transplant products and transfusion. Viral shedding from the respiratory system in the blood plasma or serum is common with coronaviruses (62). The risk for SARS-CoV-2 transmission through blood components in asymptomatic SARS-CoV-2 infected individuals is yet to be established. This problem could be overcome through improving blood biosafety protection, following standard measures for the virus inactivation in blood products, and questioning the health condition of blood donors and their relatives for a period after donation (63,64). In addition, we observed that, during COVID-19 the blood donor pool and blood supplies reduced due to the hesitation of donors.

CONCLUSION

COVID-19 is a new and serious pandemic, that has spread rapidly with a critical impact on hematology-oncology practice. Data is limited in childhood leukemia, but suggest that, management of cancer therapy during the pandemic is challenging given the higher morbidity and mortality rate in immunocompromised patients, especially if they recently received myelosuppressive chemotherapy and have comorbid medical conditions. The current rapid worldwide spread of COVID-19 necessitates identifying optimal preventive strategies and effective medical management. A clear understanding of the underlying immune response to SARS-CoV-2 infection will facilitate the development of effective treatments and vaccines to control the ongoing pandemic. Cancer clinicians and patients are critically affected and need guidance from experts and colleagues regarding reasonable changes to standard practice. We tried to review appropriate approaches for prevention, diagnosis and treatment protocols for children with cancer during the pandemic period.

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Hematologic Parameters of Patients with COVID-19 Infection

COVID-19'lu Hastalarda Görülen Hematolojik Parametreler

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ABSTRACT

SARS-CoV-2 causes primarily respiratory tract infection, but can also affect hematopoietic and immune systems. Quantitative and qualitative changes in lymphocytes, neutrophils, monocytes and platelets, are reported in infected patients. These changes are related to the severity of the disease. Lymphopenia is the most common finding in adult patients infected with SARS-CoV-2, while it is much less common in children. Leukocytosis can be detected in patients with severe infection, but rare in patients with mild to moderate infection. Thrombocytopenia or thrombocytosis can also be seen in accordance with the clinic. Dysplastic morphological changes in neutrophils and platelets can be detected in peripheral smear of patients.

Key Words: COVID-19, Hematology, lymphocyte, Neutrophil Thrombocyte

ÖZ

SARS-CoV-2 primer olarak solunum yolu enfeksiyonuna neden olmakla birlikte hematopoietik ve immun sistemlerini de etkileyebilmektedir. Enfekte olan hastalarda, lenfositler, nötrofiller, monositler ve trombositlerde kantitatif ve kalitatif değişiklikler bildirilmektedir. Bu değişiklikler ile hastalığın şiddeti arasında ilişki olduğu da gösterilmiştir. Lenfopeni, SARS-CoV-2 ile enfekte erişkin hastalarda en sık görülen bulgu iken çocuklarda çok daha az görülmektedir. Şiddetli enfeksiyonu olan hastalarda lökositoz saptanabilir, hafif-orta şiddette enfeksiyonu olan hastalarda ise lökositoz daha nadirdir. Klinik ile uyumlu olarak trombositopeni veya trombositoz da görülebilmektedir. Hastaların periferik yaymalarında özellikle nötrofil ve trombositlerde displastik morfolojik değişikler saptanabilir.

Anahtar Kelimeler: COVID-19, Hematoloji, Lenfosit, Nötrofil, Trombosit

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has rapidly evolved from an epidemic outbreak in Wuhan, China (1). World Health Organization (WHO) describes SARS-CoV-2 as a pandemic on March 11, 2020 that infecting more than one million individuals all over the world (2). The SARS-CoV-2 viruses are positive single-stranded RNA viruses and primarily manifested as a respiratory tract infection. It may be cause systemic disease including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic and immune system (3). Clinical studies showed that the most threatened population are the elderly people. Cases of COVID-19 in those aged <20 years comprise around 2% of those infected and if infected, deaths in this age group appear very rare (4).

Given the immunosuppressive nature of cancer therapies, patients with cancer have a statistically higher incidence of severe events such as intensive care unit admission, ventilation and death after contracting COVID-19 in China (5).

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We aimed to examine the hematological parameters especially in hemogram observed in the diagnosis and treatment process of patients diagnosed with COVID-19 in the light of current literature.

Lymphopenia

In laboratory examinations, lymphopenia is a common finding in COVID-19 patients (6). During the early phase of the disease, especially incubation period (ranging from 1 to 14 days) leukocyte and lymphocyte counts are normal or slightly reduced. About 7 to 14 days after the onset of the initial symptoms,

Approximately 7 to 14 days from the onset of the initial symptoms, "cytokine storm" appears with a pronounced systemic increase of inflammatory mediators and cytokines. In this instance, significant lymphopenia becomes evident (7). In a recent study of 1099 patients in China, lymphocytopenia was present in 914 (83.2%) of the patients on admission (8). Moreover, Lu et al. (9) showed that patients with lymphocytopenia have an increased risk of cytokine storm and disease severity. In many studies the mechanism of this has been shown that, lymphocytes express the ACE2 (angiotensin converting enzyme) receptor on their surface; thus COVID-19 may directly infect those cells and lead to their lysis. Furthermore, as a result of cytokine storm, interleukins such as IL-2, IL-6 and TNF-alpha levels increase, which may induces lymphocyte apoptosis (10-13). In addition, cytokine activation may be also associated with atrophy of lymphoid organs, including the spleen, and can also disrupt lymphocyte turnover (14). Development of lactic acidosis in patients with severe disease and cancer who are at increased risk for complications may also inhibit lymphocyte proliferation (15). In addition to these mechanism, medications used for the treatment of COVID-19 like steroids can also cause lymphopenia.

Huang et al.(16) showed that, in their study of 41 adults with COVID-19 infection, on admission 10 patients (25%) had leukopenia (white blood cell count less than 4×10^9/L) and 26 patients (63%) had lymphopenia (lymphocyte count < 1×10^9/L). Similarly, these results were consistent in other descriptive studies in China (17). Also in these studies, Huang et al.(16) and Wang et al. (18) emphasized a relationship between need for intensive care and lymphopenia. In addition, Wu et al. (19) showed an association between lymphopenia and acute respiratory distress syndrome (ARDS) development and increased risk of ARDS was significantly associated with increased neutrophils, which was associated with increased risk of death.

In another study, Deng et al. (20) has also been reported that patients with severe disease and fatal outcomes present with a decreased lymphocyte/white blood cell ratio both in admission. Similarly, Fan et al. (21) identified that lymphocyte count of < 0.6 x 10^9/L increases the risk for intensive care unit admission.

In children, unlike adults, lymphopenia is much less common. In Henry et al. (22) meta-analysis, lymphopenia was seen 3% of 66 pediatric patients in China.

Leukocytosis and Neutrophilia

The data on neutrophilia are incomplete and suggest that neutrophilia is an expression of the cytokine storm and hyperinflammatory state. In literature, leukocytosis and neutrophilia were generally seen in the case of bacterial infection or superinfection. A meta-analysis of the literature showed that leukocytosis was identified in 11.4% of patients with severe disease compared to 4.8% of patients with mild to moderate disease (23).

In two studies in Wuhan, patients with high troponin-T levels and myocardial injury had higher leukocyte, increased neutrophils and decreased lymphocytes (24,25).

Thrombocytopenia

Thrombocytopenia is an important indicator of COVID-19 patients and can be seen in the severe form of infection. In a study of Guan et al. (8), thrombocytopenia was observed in 36% of 1099 patients with COVID-19 infection and this finding was more prominent among severe versus non-severe cases. To support this study, a meta-analysis of nine studies has suggested that thrombocytopenia is significantly associated with the severity of the COVID-19 disease and a decrease in platelet count was more evident especially in nonsurvivors (26). In another study, thrombocytopenia was identified in up to 57.7% of patients with severe infection and 31.6% of patients with less significant symptoms (23). In the literature the studies suggest that the cause of thrombocytopenia may be due to sepsis, multiorgan failure, inhibition of megakaryocytes in the bone marrow and blocks the release of platelet, or platelet being consumed because of pulmonary thrombus formations (27).

Chen et al. reported that thrombocytopenia was seen in 12% of 99 patients and interestingly they also identified thrombocytosis in 4% patients (28).

CONCLUSION

In conclusion, COVID-19 infection has significant manifestations in the hematopoietic system. It would be better to include as many patients as possible to get a more comprehensive understanding of COVID-19 infection. Careful evaluation of laboratory indices at baseline and during the disease course can assist clinicians in formulating an appropriate treatment approach and provide intensive care to those who are in greater need.

We expect that in the months to come, more detailed studies will be forthcoming on the impact of COVID-19 infection, including the risk of infection and treatment strategies.

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Use of Convalesant Plasma in CoOVID-19 Infection

COVID-19 Enfeksiyonunda Konvalesan (İmmün) Plazma Kullanımı

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ABSTRACT

Coronavirus 2 (SARS-CoV-2), which started in December 2019 in Wuhan province in China and caused serious respiratory infections in humans, was accepted as a pandemic on March 11, 2020. The disease from SARS-CoV-2 is called COVID-19. In a short period of five months, approximately 4 million people were infected and 300 thousand people died from this disease. To date, no specific therapeutic agents or prophylaxis for COVID-19 are available, so it is among the passive immunization treatment options with the plasma of patients who recover from the disease. Convalescent plasma therapy has been used in epidemic periods in the past and has been shown to be effective. Neutralizing antibodies in plasma contributes to recovery by inactivating the virus. In the literature, there are 4 publications presenting a total of 21 patients receiving convalescent plasma. They reported that the patients benefited from the treatment of convalescent plasma and that there were no complications. Studies have been initiated about convalescent plasma all over the world and their results are interestedly awaited.

Key Words: Convalescent plasma, COVID 19, Immune plasma, SARS-CoV-2

ÖZ

Çin'de Wuhan eyaletinde Aralık 2019'da başlayan ve insanlarda ciddi solunum yolu enfeksiyonlarına neden olan Coronavirus 2 (SARS-CoV-2) çok hızlı bir yayılım göstererek 11 Mart 2020 tarihinde pandemi olarak kabul edilmiştir. SARS-CoV-2 kaynaklı hastalık tablosuna COVID-19 adı verilmektedir. Beş ay gibi kısa bir sürede yaklaşık 4 milyon kişi enfekte olmuş ve 300 bin kişi bu hastalıktan kaybedilmiştir. Günümüze kadar etkili bir profilaksi ve tedavisi bulunamayan hastalıkta iyileşen hastaların plazması ile pasif bağışıklama tedavi seçenekleri arasında bulunmaktadır. Konvalesan plazma tedavisi geçmişte salgın hastalık dönemlerinde kullanılmış, etkili olduğu gösterilmiştir. Plazmadaki nötralizan antikorlar virüsü inaktive ederek iyileşmeye katkı sağlamaktadır. Literatürde, konvalesan plazma verilen toplam 21 hastanın sunulduğu 4 yayın bulunmaktadır. Hastaların konvalesan plazma tedavisinden fayda gördüklerini ve herhangi bir komplikasyon olmadığını bildirmişlerdir. Tüm dünyada konvalesan plazmayla ilgili başlatılmış çalışmalar olup bunların sonuçları merakla beklenmektedir.

Anahtar Kelimeler: Konvalesan plasma, İmmün plazma, COVID 19, SARS-CoV-2

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INTRODUCTION

Coronavirus 2 (SARS-CoV-2), which started in December 2019 in Wuhan province in China and caused serious respiratory infections in humans, turned into a global health crisis. The disease from SARS-CoV-2 is called COVID-19 (1,2). It spread rapidly to the world in a short period of 3 months and was declared as a pandemic by the World Health Organization on 11 March 2020. According to the data of the World Health Organization, the number of patients with SARS-CoV-2 proved is 3 925 815 and the number of deaths is 274 488 in 215 countries on 10 May 2020. According to the data from ministry of health, the number of patients with SARS-CoV-2 proved is 138 657, the number of deaths is 3786 and the number of people recovering is 92 691 in our country on 10 May 2020. To date, no effective prophylaxis against SARS-CoV-2 or proven treatment options in COVID-19 have been reported. There are studies conducted with various drugs [antiviral drugs (remdesivir, favipiravir, ribavirin, lopinavir/ritonavir), antimalarial drugs (chloroquine, hydroxychloroquine) and interferon-ß], but there is currently no definitive treatment. Passive immunization (convalescent plasma transfusion) had been used outbreaks of the SARS-CoV-1 in 2003, the H1N1 influenza virus in 2009-2010, and MERS- CoV in 2012 and shown to be successful and it is usage has been raised again (3,4).

Convalescent means recovering from an illness or operation. Convalescent plasma refers to the plasma collected from individuals who recovered after infection and developed antibody. Giving the convalescent plasma transfusion to the hospitalized patients for therapeutic purposes due to active virus infection can be defined as “passive immune transfer”. Previous transfusions have been shown that passive immunization reduces damage to target organs and neutralizes pathogens directly (5-7).

It has been stated by both the World Health Organization and the American Food and Drug Administration (FDA) that it is possible that convalescent plasma, serum or immune globulin concentrates can be effective against COVID-19 infection when vaccines and/or effective anti-viral drugs are not available (8.9).

COVID-19 Immune Plasma Collection

This section was prepared by using the T.C. Ministry of Health, General Directorate of Health Services, Department of Blood and Blood Products COVID-19 Immune (Convalescent) Plasma Supply and Clinical Use Guide and the FDA’s guide to the use of COVID-19 convalescent plasma. Since COVID-19 convalescent plasma will be collected by apheresis, it should be collected from individuals who meet the donor eligibility criteria for plasma collection and donor eligibility criteria for the transfusion-transmitted infections. For this reason, it should provide the necessary conditions for “Whole Blood Donation” (8-10);

1. Short physical examination, filling the blood donor registration form, blood donor interrogation form, apheresis donor informed consent form, COVID-19 immune plasma donor interrogation form, and the “COVID-19 Immune Plasma Voluntary Donor Consent Form” which shows that COVID-19 immune plasma donation is done on a voluntary basis.
2. The donor candidates, microbiological tests (serological as HBsAg, anti-HCV, anti-HIV-1-2 and anti-syphilis Ab tests and do if HBV-DNA, HCV-RNA, HIV-1,2-RNA Nucleic Acid Amplification Scanning (NAT) test must be done.

To Become COVID-19 Immune Plasma Donor;

1. Demonstration of the presence of COVID-19 infection (PCR test positivity studied from the nasopharyngeal swab sample) or test positivity for SARS-CoV-2 antibodies if not tested at the time of suspected COVID-19.
2. At least 14 days have passed since the recovery of COVID-19 clinical findings.
3. Demonstration that COVID-19 infection has healed [At least 2 PCR test results negativity (one of the tests must have been done within the last 48 hours) from the nasopharyngeal swab samples]. If 28 days have passed since the clinical improvement, the test negativity requirement is not required (This period is recommended by the FDA as 14 days).
4. Immune plasma donors should preferably be selected from men, women who are not pregnant (birth / abortion / induced abortion), and people who have not received a blood transfusion. Women who have given birth or miscarriage and those who have had blood transfusions should be screened for HLA antibodies and shown to be negative in order to be donors.

Processes to be Applied to COVID-19 Immune Plasma Product

1. Measurement of SARS-CoV-2 neutralizing antibody titers (if possible).
   - It is recommended that the neutralizing antibody titer is ≥ 1/80 (recommended as ≥1 / 160 in the FDA guide). After the threshold value corresponding to this value has been defined in the literature with the ELISA test, those with antibody values above this threshold value should be selected.
   - If it is not possible to measure under the current conditions, the sample should be stored from the plasma taken for future measurement.
2. In order to maximize transfusion safety, it is recommended that the plasma received is subjected to “Pathogen Inactivation”.
3. Apheresis method should be chosen for plasma donation. Immune plasma donation can be made up to 3 times in a

month, once every 7-10 days, provided that the date of the first donation is accepted as the start date. In this context, 200 to 600 mL plasma can be collected from donors by ignoring the amount of anticoagulant solution. If more than 200 mL of ingredients are collected, the components should be individually labeled as a 200 mL divided component. Plasma components taken for traceability should be labeled (COVID-19 Immune Plasma) with the provision of Turk Kızılay using the ISBT coding system and witness samples should be stored in accordance with national legislation in terms of traceability.

4. COVID-19 immune plasma should be irradiated if the plasma collected after collection is to be used within 6 hours without being frozen. For the components that will not be used within six hours, freezing should be started within the first 6 hours after the completion of the apheresis process in accordance with the "National Standards for Blood Service Units" guide.

Patient Selection for COVID-19 Immune Plasma Use

There are no definitive treatment algorithms for immune plasma therapy in COVID-19 cases. For this reason, choosing the appropriate treatment becomes important. In studies conducted in China for the COVID-19 clinical course, hospitalizations were generally between the fourth and fifth days, clinical and laboratory values worsened between the seventh and tenth days, and the patient needed intensive care after the seventh and eighth days, and the patient's antibody production started during the seventh and tenth days. It is the period when it started the war against the virus and studies have shown that cytokine storm during this period. Therefore, immune plasma therapy is reported to be effective between the seventh and fourteenth days from the onset of clinical symptoms (8, 10,11). Based on these data, both the FDA and the Ministry of Health published an immune plasma treatment guide in COVID-19 cases.

According to this;

- Laboratory tests showing that COVID-19 is positive
- Severe or life-threatening COVID-19 condition

Severe disease is defined as one or more of the following:

- Persistent fever (7 days)
- Dyspnea ,
- Respiratory rate ≥ 30 / min ,
- Blood oxygen saturation 93%,
- Arterial partial oxygen pressure /inspiratory oxygen fraction <300,
- Oxygen saturation <93% despite nasal oxygen supply of 5 liters /minute and above,
- An increase in lung infiltration > 24% within 24 to 48 hours,
- Sepsis Related Organ Failure Assessment Score (SOFA Score) ≥ 2
- Blood lactate level> 2 mmol /L
- Need of a vasopressor
- Patients with rapid clinical progression, those with poor prognostic parameters (lymphopenia; increased C-reactive protein, elevated level of erythrocyte sedimentation rate, elevated level of ferritin, elevated level of lactate dehydrogenase, elevated level of D- dimer)
- Organ failure, respiratory failure, septic shock condition requiring intensive care treatment

Life-threatening disease is defined as one or more of the following:

- Respiratory failure,
- Septic shock,
- Multiple organ dysfunction or failure

Be informed by the patient or the healthcare representative.

Possible Risks of Immune Plasma Treatment

To date, immune plasma transfusion appears to be safe in patients with COVID-19. Plasma transfusion risks are the same as for any blood product transfusion (12);

- Accidental infection with the infectious pathogen,
- Severe lung injury in patients with transfusion-related acute lung injury (TRALI)
- Includes general reactions such as transfusion-associated circulatory overload (TACO). In addition, it concerns the development of antibody-dependent tissue damage and the suppression of natural antibody development against the SARS- CoV 2 virus. However, up to now, these problems have not been encountered in immune plasma transfusions against the SARS- CoV 2 virus.

COVID-19 Convalescent plasma experiences

There are 4 publications in the literature that share their experience with the use of COVID-19 convalescent plasma. Four patients presented by Zhang B and colleagues (13) gave convalescent plasma at different doses and times when they were in the shock, connected to the mechanical ventilator. They reported that all patients recovered after plasma treatment and did not see any complications related to plasma transfusion.

Duan et al.(14) reported that 10 patients with convalescent plasma had an increase in oxygen saturation and improvement in infection parameters within 3 days. 200-400 mL plasma was collected from the forty donors with the Baxter CS 300 cell separator device by apheresis method. Plasma was treated with methylene blue and light treatment for 30 min for virus inactivation. No serious complications were seen after

plasma treatment. Shen et al. (15) treated 5 COVID-19 cases, Ahn et al.(16) treated 2 COVID-19 cases with convalescent plasma. They reported that there was a clinical and laboratory improvement in cases, and no complications related to plasma transfusion developed.

Convalescent plasma therapy is used worldwide. There are 61 studies registered in Clinical Trials, which investigates the reliability, efficacy and complications of Convalescent plasma on 10 May 2020. According to the data of "uscovidplasma.org" in the USA, 7205 COVID-19 convalescent plasma transfusions were performed on 7 May 2020. Experiences in our country are also increasing and their effectiveness will be evaluated better after evaluating these data.

In conclusion, COVID-19 convalescent plasma has not yet been proven to provide clinical benefit in patients affected by this disease. It is not known whether this treatment will help COVID-19 patients or have any harmful effects, but it is one of the only treatments we currently have.

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Cytokine Release Syndrome and Treatment in COVID-19

COVID-19'da Sitokin Salınım Sendromu ve Tedavi Yaklaşımları

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ABSTRACT

The emergent outbreak of coronavirus disease 2019 (COVID-19) is a global health problem and has been recognized as a pandemic. Although COVID-19 leads to mild flu-like symptoms in most patients, the disease may cause frequently fatal, severe complications, such as acute respiratory distress syndrome and cytokine release syndrome. In these patients, defects in lymphocytic cytolytic activity trigger the proinflammatory cytokine cascade, and then "cytokine storm" begins. As a result, it leads to uncontrolled active macrophage entry into the tissues and hemophagocytosis. Here, the responses of host cells, cytokine release syndrome and the therapeutic approaches to alleviate the cytokine storm in COVID-19 will be reviewed.

Key Words: COVID-19, Cytokine Release Syndrome, Cytokine Storm, Tocilizumab

ÖZ

Yeni ortaya çıkan coronavirus hastalığı 2019 (COVID-19) küresel bir sağlık sorunudur ve pandemi olarak kabul edilmiştir. COVID-19, hastaların çoğunda hafif grip benzeri semptomlara yol açmasına rağmen, hastalık akut solunum sıkıntısı sendromu ve sitokin salınım sendromu gibi sıklıkla ölümcül, ciddi komplikasyonlara neden olabilir. Bu hastalarda lenfositik sitolitik aktivitedeki defektler proinflamatuar sitokin kaskadını tetiklemekte ve "sitokin fırtınasını" başlatmaktadır. Sonuç olarak, dokulara kontrolsüz aktif makrofaj girişine ve hemofagositoza yol açmaktadır. Burada, COVID-19'da konakçı hücrelerin yanıtları, sitokin salınım sendromu ve sitokin fırtınasını durdurmak için tedavi yaklaşımları ele alınmıştır.

Anahtar Kelimeler: COVID-19, Sitokin Salınım Sendromu, Sitokin Fırtınası, Tocilizumab

INTRODUCTION

The SARS-CoV-2 infection (COVID-19), which causes severe acute respiratory syndrome, was accepted by the World Health Organization as a pandemic on March 11, 2020 and is an important global health problem. Due to the rapid increase in the number of cases and deaths, the load on the emergency services and intensive care units is increasing day by day. Here, the definition, pathogenesis and treatment of cytokine release syndrome (CRS), a life-threatening condition in severe COVID-19, will be discussed.

Cytokine Release Syndrome

Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are life-threatening conditions with different etiological causes, which can lead to systemic hyperinflammation and rapidly progressive multisystem organ failure. HLH occurs familial (primary; pHLH) or secondary to infection, malignancy, autoimmune or autoinflammatory disease. Secondary HLH (sHLH) associated with autoimmune or autoinflammatory disease is called MAS. The mortality rate of sHLH is lower than that of pHLH. However, if sHLH is diagnosed early and effective treatment is not given, it may be life-threatening.

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Table I: Clinical and laboratory findings in cytokine release syndrome (38).

System Involvement / Findings	
General symptoms	Fever, malaise
Hematological findings	Cytopenia, coagulopathy, neutropenia, disseminated intravascular coagulation
Cardiac findings	Hypotension, arrhythmia, QT prolongation, troponin elevation, cardiomyopathy, heart failure
Lung findings	Hypoxia, tachypnea, pulmonary edema, respiratory failure
Liver / spleen	Hepatomegaly, elevated liver enzymes, hypofibrogenemia, liver failure, splenomegaly
Renal findings	Acute kidney injury
Gastrointestinal findings	Diarrhea, nausea, vomiting
Central nervous system findings	Headache, confusion, hallucination, delirium, paresis, seizure
Musculoskeletal system findings	Myalgia, arthralgia, rash, edema

In these patients, defects in lymphocytic cytolytic activity trigger the proinflammatory cytokine cascade, interleukin-1 (IL-1), IL-6, IL-18, soluble IL-2 receptor, tumor necrosis factor-α (TNF-α) and interferon-γ (INF-γ) levels increase, then "cytokine storm" begins. As a result, it leads to uncontrolled active macrophage entry into the tissues and hemophagocytosis. Similarly, there was an increase in cytokines such as IL-1, IL-6, IL-12 and TNF-α in COVID-19, and with this increase, sepsis, multiorgan failure, tissue damage and acute respiratory distress syndrome (ARDS) has been shown (1).

Cytokine release syndrome or cytokine storm can be defined as uncontrolled release of cytokines that can be triggered by viruses, bacterial components, sepsis, toxins (2). This syndrome can lead to devastating effects such as life-threatening capillary leak, tissue toxicity / edema, organ failure and shock. Resistant and persistent fever, liver dysfunction, coagulopathy, cytopenia, hepatomegaly, skin rash and neurological symptoms may occur in CRS (Table I) (3). Leukocyte, lymphocyte, platelet count, IL-6 and ferritin levels guide the determination of those at risk for CRS development in severe COVID-19 patients. Elderly patients with chronic disease were found to be the most risky group for CRS in COVID-19. CRS in children is not as common as in adults.

Pathogenesis of Cytokine Release Syndrome

The innate immune system constitutes the first line of defense against invading microbial pathogens by releasing multiple inflammatory cytokines to antagonize the pathogens. After SARSCoV-2 infection, CD4+ T lymphocytes are rapidly activated to transform into pathogenic T helper (Th) 1 cells and the production of cytokines begins. The cytokines induce inflammatory CD14+ CD16+ monocytes with high level of IL-6 and inflammation becomes evident (2, 4). These T cells and monocytes enter the pulmonary circulation, where monocytes become macrophages. It is considered that activated macrophages are the source of cells releasing the cytokines which are at the center of CRS immunopathology. CRS may lead to detrimental effects such as epithelial and endothelial cell apoptosis, vascular leakage, altered tissue homeostasis. CRS is associated with necrosis and tissue destruction, pulmonary edema, acute bronchopneumonia, alveolar hemorrhage, reactive hemophagocytosis, and ARDS (5). In autopsies of COVID-19 patients, it has been shown that infiltration of macrophages and activation of alveolar macrophages. It was found that interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes in the lungs of a patient who died due to COVID-19 (6). In addition, virus clearance from cells is impaired by suboptimal T cell response (7).

Lymphocytopenia and Cytokine Levels in Cytokine Release Syndrome

Clinical studies of COVID-19 have shown that there is lymphocytopenia and many cytokines, particularly IL-6, are significantly elevated (1,8).

In two different studies, 35 (99%) of 99 patients and 97 (70.3%) of 138 patients had lymphocytopenia (lymphocyte count <1.5x109 / L). It has been reported that lymphocytopenia can be used as a risk factor in determining cytokine storm and disease severity in these patients (9,10). It has been reported that lymphocytopenia can be used as a risk factor in determining cytokine storm and disease severity in these patients (9,

10). Yu, and Xu et al. (11) reported that lymphocytopenia and cytotoxicity are associated with the severity of hypoxemia (12).

Many cytokines levels such as IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), IFN-γ, interferon-inducible protein (IP10), macrophage inflammatory protein (MIP1), MIP1A, MIP1B, TNF-α, vascular endothelial growth factor were higher in COVID-19 patients than in healthy adults. In addition, the levels of cytokines were higher in intensive care unit (ICU) patients than non-ICU patients (1, 3). Huang et al. (13) reported that patients with severe disease have higher concentrations of G-CSF, IP-10, MCP-1, MIP1, TNF-α levels, ie cytokine storm. In another study from China, increased expression of IL-2R and IL-6 in serum predicted the

severity and prognosis of patients with COVID-19 (14). It has been shown that T cells decrease significantly (especially CD8 + T cells) and IL-6, IL-10, IL-2 and IFN-γ levels increase in severe COVID-19. In addition, neutrophil / CD8 + T cell ratio has been defined as a very strong prognostic factor in severe COVID-19 (15). Peripheral blood flow cytometric analysis showed that T cells have over activation to contribute severe immune system damage (7).

Increased cytokine levels, C-reactive protein (CRP), ferritin and lymphopenia help the clinician in diagnosing CRS in COVID-19 patients. Inflammation in the liver triggers the release of CRP release and this is known to occur in response to systemic IL-6 elevation (16). It has been reported that CRP levels in COVID-19 patients positively correlate with the size of lung lesions detected on computed tomography, which may predict the severity of the disease (17).

Treatment in Cytokine Release Syndrome

In order to control cytokine storm, it is important early diagnosis, rapid initiation of treatment, but treatment options are limited for severe COVID-19. It has not been shown that antiviral drugs such as lopinavir / ritonavir have significant benefits compared to standard treatments in patients who develop cytokine storm (18). Antiviral treatments and immunomodulatory drugs should be used together to control cytokine storm in COVID-19 patients.

As is known, corticosteroids are commonly used drugs for immunomodulatory therapy in infectious diseases. Corticosteroids are known to reduce lung inflammation in patients with pneumonia, but can also inhibit immune response and pathogen clearance. Significant benefits have not been demonstrated in respiratory tract infections caused by influenza, RSV, SARS-CoV or MERS-CoV. Higher viremia levels were found in SARS-CoV patients treated with steroids. It has also been shown to higher mortality, longer hospitalization and increased risk of secondary infections in influenza patients (19). Similarly, the use of corticosteroids in the treatment of COVID-19 is controversial as it can cause suppression of the immune system and delayed viral clearance. Zha et al. (20) demonstrated that the use of corticosteroids in mild COVID-19 patients does not affect viral clearance, hospitalization or symptom duration. On other hand, in a trial that included 201 COVID-19 patients, methylprednisolone therapy was associated with reduced the risk of death in patients with ARDS. Based on these findings, corticosteroid use is considered to be particularly effective in severe COVID-19 cases with ARDS, but it does not provide significant benefit in mild cases (21). Corticosteroids should be used only in critically ill patients at low / moderate doses (1-2 mg / kg / day) for a short time (3-5 days) (22).

The use of chloroquine and hydroxychloroquine has been found to be effective in the treatment of COVID-19. In February 2020, more than 100 patients diagnosed with COVID-19 had positive results with chloroquine phosphate (23). The efficacy of hydroxychloroquine treatment in 20 patients with COVID-19 patients has been demonstrated in an open-label non-randomized clinical study in France (24). Both chloroquine and hydroxychloroquine are weak bases and accumulate in acidic organelles; they can increase endosomal / lysosomal pH and inhibit viral replication (25). Both drugs can inhibit major tissue suitability complex II expression, antigen presentation, and immune system activation via Toll-like receptor and cGAS-STING signaling in B, T and other immune cells (26). The major proposed immunomodulatory mechanisms of both drugs are the following: inhibition of cytokine production, reduced levels of chemokines, inhibition of micro-RNA expression, decreased TH17-related cytokines, upregulated levels of IFN-α and IL-2 and IL-10, inhibition of cytotoxic T cell and self-reactive CD4+ lymphocyte activities. As a result, they can reduce the production of proinflammatory cytokines such as IL-1, IL-6, IFN-γ and TNF-α, which are involved in CRS (26).

The use of immunomodulatory agents that directly target cytokines in severe COVID-19 patients may contribute to control symptoms related to hyperinflammation (27). It has been reported that the increase in IL-6 levels in the blood of COVID-19 patients predicts fatal outcome (28). Herold et al. (29) showed that patients with IL-6 levels of ≥ 80 pg / ml had a 22-times higher risk of respiratory failure than those with low IL-6 levels. In addition, IL-6 levels have been shown to be 3-fold higher in ICU than non-ICU patients in a metanalysis evaluating the results of ten studies involving data from 1700 COVID-19 patients (30). IL-6 binds to transmembrane IL-6 receptors (mIL6R) and soluble IL-6 receptors (sIL-6R), and this complex combines with the signal transduction component gp130 to activate the inflammatory response. Tocilizumab, a specific monoclonal antibody that blocks IL-6, specifically binds to sIL-6R and mIL-6R and thereby blocks signal transmission (31). Tocilizumab, sarilumab, siltuximab are IL-6 antagonists with different pharmacologic properties. In recent years, since anti-IL-6 drugs such as tocilizumab and sarilumab have been used in the treatment of rheumatological diseases, it has been focused on these treatment options for SARS-CoV-2 and it has been observed that the hyperinflammatory syndrome in severe SARS-CoV-2 infection can be controlled. In a study from China, a single dose (400 mg) of tocilizumab was used in 21 infected patients with SARS-CoV-2, and fever was controlled within 5 days, a rapid decrease in CRP, oxygen requirement, and improvement in lymphocyte counts and radiological findings (32). However, in this study, the lack of a control group, treatment of all patients with lopinavir and methylprednisolone prior to receiving tocilizumab is considered as an important limitation. There is emerging evidence that tocilizumab may also be useful in COVID-19. It has been suggested to be used in patients with multiple lesions in the lungs, high IL-6 level and critical disease (22).

However, clinical experience and studies with the use of tocilizumab in viral diseases are very limited. In a study on patients with juvenile idiopathic arthritis infected with influenza A, reduced fever and level of CRP were demonstrated in patients who received tocilizumab compared with patients who did not receive tocilizumab (33).

It should be noted that tocilizumab increases the risk of opportunistic infections (34). Therefore, it is necessary to monitor patients for potential side effects. In addition, high costs are a problem for the wide use of tocilizumab in the treatment of COVID-19 in low- or middle-income countries.

Although a monoclonal antibody against IL-6 receptor, is shown to be effective in treating CRS, the results of studies currently ongoing with sarilumab, tocilizumab, combination of tocilizumab and favipiravir are expected.

IL-1 is another proinflammatory cytokine that increases in CRS. Anakinra and other IL-1R antagonists are used in the treatment of autoinflammatory diseases, systemic juvenile idiopathic arthritis and MAS. It is predicted that it may be beneficial in CRS patients with high IL-1 levels (35).

The antibody against GM-CSF has also been shown to be effective in the treatment of cytokine release syndrome (36).

JAK-STAT signaling pathway; it is a critical component of cytokine receptor systems, and many HLH-related cytokines use this pathway. Therefore, JAK inhibitors such as tofacitinib and baricitinib can reduce hyperinflammation caused by CRS. However, their effectiveness in the treatment of COVID-19 patients is still uncertain (37). Moreover, it should be noted that these inhibitors also inhibit the activity of inflammatory cytokines, such as INF-α, which are known to play an important role in viral clearance (37).

CONCLUSIONS

Severe COVID-19 can cause hyperinflamation and cytokine release syndrome. Although it is not common in childhood as in adults, early diagnosis and treatment is very important due to the high mortality rate. In severe COVID-19 patients, CRP, ferritin, D-dimer increase and cytopenia should be monitored as signs of hyperinflamation. These values will be useful in identifying patients for whom cytokine suppression is required.

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COVID-19 Management in Children: Approach in Pediatric Cardiology

Çocuklarda COVID-19 Yönetimi: Çocuk Kardiyolojide Yaklaşım

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ABSTRACT

In children, cardiac involvement can be observed during the course of COVID-19, which is mostly mild, and COVID-19 may develop in children who have previously been known to have congenital or acquired heart disease. The subject of this article is how these children should be evaluated cardiacly, and how the follow-up and treatment of children with heart disease will be managed during the pandemic. Considering the articles and guides published in the literature, some determinations were made and the suggestions developed were presented in this article.

Key Words: Approach, Cardiology, Children, COVID-19, Management

ÖZ

Çocuklarda çoğu zaman hafif seyreden COVID-19 seyri sırasında kardiyak tutulum görülebileceği gibi, daha önce doğumsal yada edinsel kalp hastalığı olduğu bilinen çocuklarda da COVID-19 gelişebilir. Bu çocukların kardiyak açıdan nasıl değerlendirilmesi gerektiği, ayrıca kalp hastalığı bulunan çocukların takip ve tedavilerinin pandemi süresince nasıl yönetileceği bu makalenin konusudur. Literatürde yayınlanmış olan makale ve rehberler dikkate alınarak bazı saptamalar yapılmış ve geliştirilen öneriler bu yazıda sunulmuştur.

Anahtar Kelimeler: COVID-19, Çocuklar, Kardiyoloji, Yaklaşım, Yönetim

INTRODUCTION

COVID-19 is mostly mild in children. Even if children are asymptomatic, there is a high level of contamination (1-14). Cardiac involvement during COVID-19 in children is extremely rare and is often accompanied by multiple organ failure. However, the number of infected children is increasing day by day and new data on cardiac involvement are obtained (15-17). The common idea in the guidelines published recently on how to manage COVID-19 in children is that unusual (out of routine) approaches should be applied during the pandemic (18-30). In this process, how to use hospital resources more effectively, which patient groups will be prioritized, how to perform patient examination, electrocardiography (ECG) and echocardiography (ECHO) evaluation, as well as how to protect patients and health personnel during interventional and surgical procedures are important issues. In this article, data from current literature and suggestions on how the process should be managed in children will be presented.

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PEDIATRIC CARDIOLOGY SERVICES DURING PANDEMIC

During the pandemic, routine polyclinic controls should be postponed, and it should be ensured that patients apply to the hospital only in emergency situations. Patients who have been diagnosed and started a specific treatment should be followed up remotely, and they should be asked to come to the hospital when necessary. Every patient admitted to the hospital should be considered as suspected COVID-19, social distance should be preserved while taking history, and protective equipment (mask, gloves, overalls, face shield) should be used during physical examination. Meanwhile, patients and their relatives should be provided to wear masks (1,2,18,19).

Routine ECG and ECHO evaluation is not recommended during pandemic. Protective equipment containing high-level masks (such as FFP1/N80, FFP2/N95 or FFP3/N100) should be ensured, especially when performing ECHO, because of long-term close contact with the patient will be necessary, taking into account that children are mostly asymptomatic and that children who are restless and crying will spread a lot of droplets around them. Echocardiography device, probes and examination table should be cleaned with soapy water after each procedure and then disinfected. Also, rooms, devices and probes used for patients diagnosed with COVID-19 should be separated. Since the risk of contamination will be very high during transesophageal echocardiography (TEE), all TEE procedures should be postponed except for emergencies (24).

Cardiac catheterization is not recommended during pandemic except in emergencies. The procedures of patients in the semi-elective diagnostic group can be delayed as much as possible (several months) depending on the patient load. The procedures of patients in the elective diagnostic group should be postponed absolutely. Urgent, semi-elective and elective diagnostic groups are presented in Table I. It is very important for angiography team to enter the procedures with flexible working order in terms of protection from contamination. Patients and their relatives who are scheduled for cardiac catheterization should be questioned for the symptoms of COVID-19, and patients and relatives with symptoms should be tested. Informed consent should also be obtained from patients' relatives that they have been informed about the pandemic process as well. If the patient's test result is negative, it is recommended that only anesthesia team use protective equipment, if positive, all angio team should use high-level protective equipment, and if possible, the procedure should be performed in a negative pressure room (21,22,25). General anesthesia should be preferred in order to minimize contamination and reduce the patient's cough and secretions as much as possible. It should be kept in mind that resuscitation may be required during cardiac catheterization, so relevant guidance suggestions should be applied in this regard (26-28).

Electrophysiological study, ablation, pacemaker and implantable cardioverter defibrillator (ICD) applications should be planned separately for the relevant diagnostic groups during the pandemic. Urgent, semi-elective and elective diagnostic groups for rhythm studies in children are presented in Table II. It is recommended that patients who have been ablated or who have been implanted with pacemaker or ICD be discharged as soon as possible (within the first 24 hours if possible) (29).

Surgery of children with heart disease, which is accepted as one of the co-morbid conditions in which the course of COVID-19 is expected severe, should be postponed unless it is urgent. The operations of patients in the semi-elective diagnostic group should be planned in a suitable period. Urgent, semi-elective and elective diagnostic groups for cardiac surgeries to be performed in children are presented in Table III. Patients who develop COVID-19 should be told about the morbidity and mortality could be higher than expected during the heart surgery and intensive care follow-up, and there is also possibility of getting the infection in the hospital, and informed consent should be obtained from patients' relatives that they are informed about that issue as well. Virus test should be performed to patient and accompanying person. Practices

Table I: Urgent, semi-elective and elective groups for cardiac catheterisation during pandemics.

URGENT (Immediately or in 1-2 weeks)	SEMI-ELECTIVE (In 1-3 months)	ELECTIVE (More than 3 months)
Pericardiosentesis TGA – Balloon atrial septostomy, HLHS – Atrial septal decompression ECMO – Atrial septal decompression APCA occlusion – Hemoptysis Duktal stent – PDA dependent KHD Balloon or stent to RVOT Critical AS/PS – Balloon valvuloplasty IVS/PA – Valve perforation PDA closure in prematures OHT – Biopsy in acute rejection	Pulmonary vein stenosis – HF or PH Large PDA – HF or PH Large VSD – HF or PH Severe AS Severe PS Severe aortic coarctation Severe conduit stenosis Pre-Glenn	Secundum ASD closure VSD closure PDA closure Moderate AS Moderate PS Postoperative moderate or severe PR Pre-Fontan OHT – Rutine biopsy

APCA: *Aorticopulmonary collateral artery,* ***AS:*** *Aortic stenosis,* ***ASD:*** *Atrial septal defect,* ***CHD:*** *Congenital heart disease,* ***ECMO:*** *Extracorporeal membrane oxygenation,* ***HF:*** *Heart failure,* ***HLHS:*** *Hypoplastic left heart syndrome,* ***IVS/PA:*** *Pulmonary atresia with intact ventricular septum,* ***OHT:*** *Orthotopic heart transplantation,* ***PDA:*** *Patent ductus arteriosus,* ***PH:*** *Pulmonary hypertension,* ***PR:*** *Pulmonary regurgitation,* ***PS:*** *Pulmonary stenosis,* ***RVOT:*** *Right ventricular outflow tract,* ***TGA:*** *Transposition of great arteries,* ***VSD:*** *Ventricular septal defect*

Table II: Urgent, semi-elective and elective groups for electrophysiologic study during pandemics.

URGENT (Immediately or in 1-2 weeks)	SEMI-ELECTIVE (In 1-3 months)	ELECTIVE (More than 3 months)
Pacemaker implantation ICD implantation Transcatheter ablation – Resistant case Infected pacemaker/lead extraction Cardioversion – Resistant case	Transcatheter ablation – Hemodynamically stabil SVT/VT Pacemaker replacement	Transcatheter ablation – Stabil case Diagnostic EPS

EPS: *Electrophysiologic study,* **ICD:** *Implantable cardioverter defibrillator,* **SVT:** *Supraventricular tachycardia,* ***VT:*** *Ventricular tachycardia*

Table III: Urgent, semi-elective and elective groups for cardiac surgery during pandemics.

URGENT (Immediately or in 1-2 weeks)	SEMI-ELECTIVE (In 1-3 months)	ELECTIVE (More than 3 months)
Pericardial tamponade - Drainage	Non-obstructive TAPVC	
Ductus dependent systemic circulation	TGA with large VSD	
(AI, HLHS, severe AC, critical AS)	Truncus arteriosus	
Ductus dependent pulmonary circulation	APW	ASD closure
(PA, critical PS)	Complete AVSD	Partial AVSD
Simple TGA	Tetralogy of Fallot with spell	VSD closure
Obstructive TAPVC	Pulmonary banding	PDA closure
Severe cyanotic CHD	Large VSD – HF or PH	Tetralogy of Fallot
Severe Shone complex	Large PDA – HF or PH	Glenn operation
Large PDA in prematures	Infective endocarditis	Fontan operation
Postoperative revision	Cardiac mass	
ECMO/assists device requirement	LVOT obstruction	
OHT	HLHS stage II	

AC: *Aortic coarctation,* ***AI:*** *Aortic interruption,* ***APW:*** *Aorticopulmonary window,* ***AS:*** *Aortic stenosis,* ***ASD:*** *Atrial septal defect,* ***AVSD:*** *Atrioventricular septal defect,* ***CHD:*** *Congenital heart disease,* ***ECMO:*** *Extracorporeal membrane oxygenation,* ***HF:*** *Heart failure,* ***HLHS:*** *Hypoplastic left heart syndrome,* ***LVOT:*** *Left ventricular outflow tract,* ***OHT:*** *Orthotopic heart transplantation,* ***PA:*** *Pulmonary atresia,* ***PDA:*** *Patent ductus arteriosus,* ***PH:*** *Pulmonary hypertension,* ***PS:*** *Pulmonary stenosis,* ***TAPVC:*** *Totally abnormal pulmonary venous connection,* ***TGA:*** *Transposition of great arteries,* ***VSD:*** *Ventricular septal defect*

regarding the use of protective equipment during surgery are the same as in cardiac catheterization. The operations should be done in rooms with negative pressure as much as possible. The room should be disinfected with ultraviolet rays after surgery (30). In the course of COVID-19, the relevant guideline recommendations on extracorporeal membrane oxygenation (ECMO) support practices and advanced life support in children should be implemented (27,28).

Although it is predicted that COVID-19 may progress more severely in children with hemodynamically significant congenital or acquired heart disease, no scientific data supporting this idea has been published yet. It is recommended that patients with COVID-19 have a closer follow-up and be hospitalized at an earlier stage (20,21).

The agent of COVID-19, SARS-CoV-2 virus is known to have high penetration into tissues with high angiotensin converting enzyme-2 (ACE2) expression (heart, lung). Although ACE2 expression is predicted to increase in tissues and increase viral damage in this way in patients using ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB), scientific data supporting this view have not been published yet. Therefore, no consensus has been reached on discontinuation of these medications in patients taking ACEI or ARB (hypertension, heart failure, valve regurgitation) (16, 20,21).

MANAGEMENT OF CHILDREN WITH COVID-19

Cardiovascular system examination is performed with vital signs (body temperature, heart rate, respiratory rate, blood pressure and oxygen saturation). In the presence of findings suggesting cardiac involvement (heart failure, irregular rhythm), ECG and ECHO evaluation are recommended. The corrected QT (QTc) should be calculated since drugs such as hydroxychloroquine and azithromycin, which are frequently used in the treatment of patients, can lead to QT prolongation and arrhythmia. Cardiac troponin level in the presence of findings indicating myocardial damage at ECG, and BNP level in patients with signs of heart failure or myocardial dysfunction at ECHO, should be studied. Routine and unnecessary ECHO evaluation should be avoided to prevent transmission from patient to physician and also to other patients as there will be prolonged close contact while performing ECHO (24).

In children with COVID-19, cardiac involvement may appear as myocardial damage or rhythm disturbance. In patients, hypoxic damage due to severe lung disease, multiple organ failure and shock due to systemic inflammatory response, and

myocardial damage due to acute viral myocarditis can be seen. Acute myocardial damage is often subclinical in children. In case of progressive or severe damage, heart failure or rhythm disturbances may occur. Patients with severe lung disease may develop right heart failure and pulmonary hypertension. Treatment approaches applied in other viral myocarditis are used in treatment. Intravenous immunoglobulin (IVIG) therapy can be beneficial with both antiviral and immunomodulatory effects. Routine troponin measurement is not recommended for patients with COVID-19 unless evidence suggesting myocardial damage develops. Likewise, routine natriuretic peptide measurement is not recommended for patients without heart failure findings. However, serial monitoring of these biomarkers in patients with severe course can provide information regarding prognosis (3,15,17).

In these patients, rhythm disturbances (such as QT prolongation) may be seen during systemic inflammatory process or as a side effect of some drugs (lopinavir/ritonavir, hydroxychloroquine, azithromycin) used in the treatment of COVID-19. Patients with congenital long QT duration, electrolyte imbalance (hypopotasemia, hypomagnesemia), using another QT-prolonging drug, other heart disease (cardiomyopathy, arrhythmia), kidney or liver failure should be regularly followed-up for QT prolongation.

QT measurement should be done 2-3 hours after the drug is administered. If the QTc duration is longer than 500 ms for those with a QRS duration below 120 ms, and longer than 530 ms for those with a QRS duration above 120 ms, or if the QTc duration has prolonged longer than 60 ms, azithromycin treatment should be discontinued and the hydroxychloroquine dose should be reduced. If QTc prolongation continues at this level, hydroxychloroquine treatment should also be terminated. If there is at least one of the above mentioned risk factors, outpatient follow-up is not recommended. If the QTc duration is over 460 ms at ECG, obtained 2-3 hours after the drug is taken on the 3rd day of treatment, in patients who do not have risk factors and are monitored on an outpatient basis, daily QTc measurement is recommended. In the follow-up, drug reduction and treatment termination criteria are applied in the same way (31-33).

It is also known that, when hydroxychloroquine is used for a long time, it may cause myocardial damage. In addition, hydroxychloroquine and some antiviral drugs (ribavirin) can increase the blood levels of some beta-blocker and anticoagulant drugs, respectively (31,33).

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Adverse Drug Reactions During COVID-19 Treatment

COVID-19 Tedavisinde İstenmeyen İlaç Reaksiyonları

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ABSTRACT

Adverse drug reactions are unintented and harmful reactions to drugs. Coronavirus disease 2019 (Covid-19) has been widely spread. Although many drugs are used in the treatment of COVID-19, there is still no specific treatment with proven reliability and effectiveness and there are many studies to find effective treatment. Attention should be taken regarding the properties, interactions and undesired drug reactions of drugs used in the treatment of COVID-19. The aim of this review is to draw attention to adverse drug reactions of the drugs that are being used in COVID-19 treatment.

Key Words: Adverse effect, Covid-19, Drug hypersensitivity, Treatment

ÖZ

İstenmeyen ilaç reaksiyonları ilaç kullanımında ortaya çıkan istenmeyen, zararlı etkilerdir. Coronavirus hastalığı 2019 (Covid-19) tüm dünyaya yayılmıştır. COVID-19 tedavisinde birçok ilaç kullanılmasına karşın, güvenilirliği ve etkinliği kanıtlanmış spesifik bir tedavi henüz yoktur ve etkili tedaviyi bulmak için çalışmalar devam etmektedir. COVID-19 tedavisinde kullanılan ilaçların özelliklerine, etkileşimlerine ve istenmeyen ilaç reaksiyonlarına dikkat edilmelidir. Bu derlemenin amacı COVID-19 tedavisinde kullanılan ilaçların istenmeyen ilaç reaksiyonlarına dikkat çekmektir.

Anahtar Kelimeler: Yan etki, Covid-19, İlaç hipersensitivite, Tedavi

INTRODUCTION

A cluster of acute respiratory illness, known as novel coronavirus (2019-nCoV) occured in Wuhan and spread all over the world. The COVID-19 pandemic is widespread in our country as well as all over the world. Although many drugs are used in the treatment of COVID-19, there is still no specific treatment with proven reliability and effectiveness and there are many studies to find effective treatment. Attention should be taken regarding the properties, interactions and undesired drug reactions of drugs used in the treatment of COVID-19. Side effects and drug hypersensitivity reactions that occur during the use of drugs are undesirable drug reactions.

Classification of Adverse Reactions to Drug

Adverse drug reaction (ADR) is a harmful, unintentional and undesired response to a drug which occurs while using in humans for diagnosis, prophylaxis and treatment. ADRs occur in 3-6% of patient admissions and occur in about 10-20% of all hospitalized patients (1). It varies according to age, drug classes and drug prescription habits.

Adverse drug reaction is classified in two types: A-type (predictable) and B-type (unpredictable) reactions. Type A reactions are the result of the pharmacological action of the drug and therefore they are dose-dependent and predictable. They are the most common reactions (70-80%). Type B reactions are unpredictable, usually non-dose-dependent and

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seen in sensitive patients. They are representing 15-20% of all ADRs but they are often severe and carry risk for mortality and morbidity (1). The classification of ADR is shown in Figure 1 (2).

Drug hypersensitivity reactions (DHRs) are defined as the emergence of objective sypmtoms or signs initiated by exposure to a defined drug at a dose tolerated by other people. They are seen in more than 7% of general population (1). DHR can be allergic or non-allergic. Allergic reactions are commonly IgE mediated (type I) and T-cell mediated (type IV). Rarely, they are mediated by cytotoxic (type II) and immune complex (type III). Gell and Coombs classification adapted to drug reactions are shown in Table 1 (3). In non-allergic reactions, immunologic mechanism has not been proved. The mechanism include nonspecific histamin release, bradykinin acumulation, complement activation, arachidonate metabolism alteration and pharmacological interaction (PI mechanism) (1)

Clinical Phenotype of Drug Hypersensitivity Reactions

Clinical characteristics and timing are used for phenotyping of drug hypersensitivity (3). Drug Hypersensitivity Reactions can be divided into two goups based on the interval between drug intake and the onset of the symptoms. Immediate reactions were defined as those occurring within 1-6 hour after drug intake and non-immediate as occuring any time from 1 hour, commonly after many days of treatment. Immediate reactions can be IgE mediated or non-immunologic mechanism and commonly shows itself with urticaria, angioedema or anaphylaxis. Non-immediate reactions are commonly mediated by type IV allergic reaction or by the PI mechanism and usually show itself with maculopapuler exanthems and delayed urticaria. In non-immediate reactions, internal organs can also be affected (1).

The most common manifestation of drug allergy is cutaneous reactions. Many phenotypes can be seen such as maculopapular exanthems, urticaria, angioedema (4). The typical signs of immediate-type reactions are erythema, urticaria and angioedema. Anaphylaxis is an immediate reaction that involves more than one system; skin (pruritus, urticarial, angioedema, erythema), gastrointestinal system (nausea, vomiting, abdominal pain and/or diarrhea), respiratory system (rhinoconjuctivitis, dyspnea, wheezing and/or coughing) and cardiovascular system (drop of blood pressure, tachycardia, fainting and unconsciousness) (1). The most common manifestation of non-immediate DHR is maculopapular exanthem. Also delayed urticaria and angioedema may be seen. Fixed drug eruption is a non-immediate DHR that is characterised by purpelish well demarcated macules. Vasculitis is a non-immediate reaction that is characterised with palpable purpuric macules found mostly in legs. Also fever, arthralgias, lymphadenopathy, headaches, abdominal pain, hematuria or peripherial neuropathy can be seen (1).

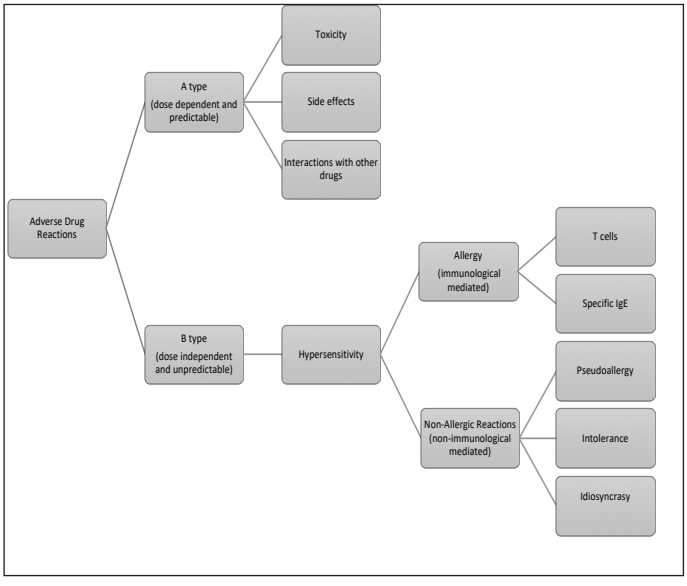

Figure 1: The Classification of Adverse Drug Reaction (2).

In non-immediate reaction, additional to skin rashes, there may be involvement of internal organs (including hepatic, pulmonary, renal and hematologic systems) and the extent of blood eosinophilia. Acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, fixed drug eruption, photosensitivity are rare (5). The most severe drug reactions are identified as severe cutaneous adverse reactions (SCAR) that contain; Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS or DIHS for Drug Induced Hypersensitivity Syndrome), acute generalized exanthematous pustulosis (AGEP), and Stevens Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN). SCAR mostly have multiorgan involvement (4).

Diagnosis and Management of Drug Hypersensitivity Reactions

The diagnostic management should begin with a detailed clinical history that includes description of symptoms, the time interval between symptoms and drug intake, the dose and administration way of drug. The administration of culprit drug must be stopped immediately and must perform detailed physical examination mast be performed and check for danger signs such as bullous lesions of mucosal locations and involvement of internal organs. The list of danger signs are shown in Table II (3). Complete blood cell, liver and renal function tests, serum tryptase level must be performed according to the type of reaction.

Treatment of Drug Hypersensitivity Reactions

The main theraphy of DHR is to discontinue the drug. Also monitoring for fever, blood eosinophilia, proteinuria, arthralgia, lymphadenopathy, and hepatitis should be done. Anaphylactic reactions must be treated with adrenaline. Exfoliative syndromes, including SJS and toxic epidermal necrolysis (TEN), and any drug rash involving mucosal surfaces, commmonly need hospitalization (6).

Table I: Gell and Coombs classification adapted to drug reactions (5).

Type	Type of Immune Response	Pathophysiology	Clinical Symptoms	Chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylaxis, Urticaria, Angioedema, Bronchospasm	1-6 Hour
II	IgG, Complement	Cytotoxic	Cytopenia	5-15 day
III	IgG, IgM and Complement /FcR	Immun Complex Deposition	Serum Disease, Vasculitis	7-8 day 7-21 day
IVa	Th1 (IFN-y)	Monocytic Inflamation	Eczema	1-21 day
IVb	Th2 (IL-4, IL-5)	Eosinophilic Inflamation	Maculopapular exanthema, DRESS	1 to several days 2-6 week
IVc	Cytotoxic T cel (Perforin, Granzyme)	Keratinocyte Death	Maculopapular, Pustular exanthema fixed drug eruption SJS/TEN	1-2 day 1-2 day 4-28 day
IVd	T cell (IL-8/CCL8)	Neutrophilic Inflamation	AGEP	1-2 day/could be longer

Avoiding the culprit drug and cross reactive drugs are recommmended (7). In selected cases, desensitization can be done (7).

Drugs used in Covid-19 Treatment

Diagnosis and treatment approaches in our country are carried out according to the COVID-19 (SARS-CoV2 Infection) guide created by the Scientific Committee of the Ministry of Health. In this guide, treatment recommendations are based on the evaluation of available evidence, clinical study protocols, and expert opinions in cases of no evidence. In line with the treatment schemes in the COVID-19 guide, hydroxychloroquine, azithromycin, oseltamivir, lopinavir/ritonavir and favipiravir are used in treatment. In addition, the use of tosilizumab (anti-IL6R monoclonal antibody), anakinra (recombinant IL-1R antagonist) are recomended among the patients with macrophage activation syndrome during the course of COVID-19 infection. For coagulation disorders that may develop with MAS and sepsis, heparin treatment is being recommended (8).

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug and approved by the U.S. Food and Drug Administration (FDA) for COVID-19 (9). Beside being antimalarial drug, it has been used in the treatment of rheumatic diseases and connective tissue diseases due to it's immunomodulatory effect. In COVID-19, treatment mechanisms may include inhibition of viral enzymes, viral DNA and RNA polymerase, viral protein glycosylation, new virus particle transport, and virus release. Other mechanisms may also include ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release. It is taken in oral administration (10).

Common side effects are risk of cardiac arrythmias (QT prolongation) and risk of retinal damage (particularly in long term use) (10). Chloroquine and hydroxychloroquine are highly toxic in overdose that are manifested with cardiovascular collapse and central nervous system toxicity (11). In patients having hepatic and renal failure, the serum level of hydroxychloroquine may icrease, so it must be taken in consideration (12). It should not be used in patients with hereditary galactose intolerance, glucose-galactose malabsorption (12).

Cardiovascular effects

Hydroxychloroquine treatment can cause significant QT prolongation and increasing risk of Torsade de Pointes (TdP) even at therapeutic doses. Other electrocardiographic changes may develop like T-wave inversion and depression (13). The arrythmia risk is higher especially in elderly patients with cardiac comorbidity, using other drugs that prolong QT, and with electrolyte disorders. For this reason, it is necessary to make a risk assessment for QT prolongation in patients who are receiving hydroxychloroquine due to COVID-19 and, if it is necessary, decide with a cardiology consultation (8).

The American Heart Association has listed hydroxychloroquine as agent that can cause direct myocardial toxicity and exacerbate underlying myocardial dysfunction (14). Hydroxychloroquine treatment is contraindicated in patients having congenital long QT syndrome and in those who have a prior history of TdP (13).

With using azithromycin treatment, the risk of QT prolongation is increasing. These patients who take the both treatment, must be checked every day with electrocardiogram (ECG). When cardiotoxic effect is seen in ECG, firstly azithromycin treatment must be stopped and later the dosage of hydroxychloroquine must be decreased, if the toxic effect is continuing, hydroxycloroquine must be stopped (12). In a recently published study about Covid 19 patients who had hydroxychloroquine and azithromycin combination treatment, patients had a 15%-20% increased risk of chest pain or heart failure and a twofold increased risk of cardiovascular mortality in the first month of treatment (15). In another study, 191 patients received hydroxychloroquine and 119 also azithromycin treatment for Covid 19. The maximum QTc during treatment was significantly longer in the combination group than the monotherapy group. Seven patients (3.5%) discontinued these medications due to

Table II: Danger Signs in Drug Hypersensitivity (5).

Immediate reaactions	Non-immediate Reactions
Sudden onset of generalized pruritus	Centrofacial edema
Pruritus in palm-soles of feet, genital area, ears and head	Skin blisters, bullae
Dysphonia	Painful skin
Dysphagia	Mucosal involvement
Inspiratory dyspnea	Pustuler exanthem
Cough	Atypical target lesions
Conjonktival hiperemia	Fever >38.5
Reduced blood pressure	Generalized erythema
	Leucopenia, thrombopenia
	Renal dysfunction (urea, creatinin□)
	Lymphadenopathia (>2 sites)
	Blood count (eosinophilia, atypical lymphocytes)
	Liver function test (liver transaminase□)
	Proteinuria
	Hypocomplementemia

QTc prolongation (16). In two studies, it was shown that both using hydroxychloroquine alone or combination therapy with azithromycin caused QT prolongation (17,18).

In a recently published case report, after the third day of hydroxychloroquine treatment, a 60 year old woman without having cardiac disease, developed a right bundle branch block and prolonged electrocardiographic QT interval (QTc: 631 ms) which then resolved with discontinuation of theraphy (19).

In conclusion, based on available data, hydroxychloroquine can cause arrhythmias, atrioventricular block, bundle branch block, QT prolongation and TdP. It must be used in attention with ECG monitoring.

Ocular effects

The retinal damage risk is increased in patients who take more than 6.5mg/kg/dose per daily, having over 200mg cumulative dosage, older 65 years age, having renal failure and visual acuity below 6/8 (12). Major risk factors for retinopathy are having hidroxychloroquine cumulative dose >1000g, duration of use >5 years, renal impairment, tamoxifen use and having macular disease (20).

In a study focused on ocular adverse effects with hydroxychloroquine various doses, there was no adverse ocular event at 6 week with Hydroxychloroquine treatment at 400mg/day, 800mg/day, and 1,200mg/day dosage (21).

In Covid-19 treatment, hydroxychloroquine is being used for a short time. Therefore no ocular adverse effect is expected if there is no risk factor of host.

Hypoglicemia

The basis of hypoglicemia effect is including reduced insulin clearance, increased insulin sensitivity and pancreatic insulin release (11). Using antidiabetics with hydroxychloroquine can cause rarely life threatening loss of consciousness and hypoglycemia (12). If hypoglicemia develops, drug must be stopped and supplemental glucose or parenteral dextrose must be administered as needed (11).

Skeletal system side effects

In long term use of this drug, it may cause weakness and periodic examination of skeletal muscle and tendon reflexes must be done (12).

Hematologic

In G6PD patients, it is known that antimalarial drugs are causative of oxidative hemolysis but in some studies it is shown that chloroquine and hydroxychloroquine are less likely to do (11). In a study, 11 rheumatology patients with established G6PD deficiency, hydroxychloroquine-related hemolysis was not experienced over more than 700 months of treatment (22). In G6PD patients, caution must be taken in consideration (10).

Neuropsychiatric side effects

Hydroxychloroquine can cause a wide spectrum of neuropsychiatric manifestations, including agitation, insomnia, confusion, mania, hallucinations, paranoia, depression, catatonia, psychosis and suicidal ideation. These can occur at all ages, in acute or chronic usage and in patients with and without a history of mental illness. Clinicians should take attention for new or worsening neuropsychiatric symptoms while using in patients who already have mental illness (11).

Cutaneous side effects

With using hydroxychloroquine, cutaneous reactions may occur. The cutaneous reactions may be rash, pruritus, pigmentation disorders in skin and mucous membranes, hair color changes,

alopecia. It is not recommended in psoriasis and porphyria because they may be exacerbated by using hydroxychloroquine treatment (23).

In newly published case report, in a Covid 19 patient having psoriasis, at the fourth day of hydroxychloroquine treatment, the patient had an exacerbation of silver-scaled psoriatic plaques spread quickly all over the body (24).

Drug Hypersensitivity Reactions

Hydroxychloroquine generally have safe profiles but cutaneous side effects can occur. It's cutaneous side effects ranges from mild skin reactions to severe cutaneous drug eruptions (25) Chloroquine and hydroxychloroquine have been implicated in severe cutaneous adverse reactions, including SJS, TEN, and DRESS. They should be considered in patients with new-onset fever, exanthem or mucositis in the weeks after the begin of treatment, especially when accompanied by new hematologic abnormalities (such as lymphopenia, eosinophilia or atypical lymphocytosis) and liver or kidney failure even it is a rare condition (11).

Newly, a severe cutaneous drug reaction resembling AGEP triggered by hydroxychloroquine treatment in Covid-19 patient has been documented (26).

Drug-Drug interactions

Genetic variability in metabolism of these drugs can influence their safety and effectiveness. Both chloroquine and hydroxychloroquine are metabolized by hepatic cytochrome P450 enzyme 2D6 (CYP2D6), the expression of which differs among patients as the result of genetic polymorphisms. This genetic variability influences the response to treatment as well as the risk of adverse events. There are interactions with many drugs such as azithromycin, cimetidine, insulin, antidiabetic drugs-insulin, cyclosporin, moxifloxacin, rifampicin, antiepileptic drugs, antiarrhythmic drugs, rifampicin and niacin etc (27).

Azithromycin

Azithromycin is an antibacterial. Macrolides may have immunomodulatory effect in pulmonary inflammatory disorders and they can decrease the excessive cytokine production related with respiratory viral infections (10).

The main side effect is cardiac toxicity (QT prolongation). In patients with long QT, hepatic and renal failure, azithromycin should not be used (10). The side effects can be classified as gastrointestinal (vomitting, feeding intolerance, abdominal tenderness, diarrhoea), respiratory (respiratory distress, bronchopulmonary dysplasia), central nervous system (intraventricular hemorrhage, abnormal hearing, PVL), hepatobiliary (elevated transaminase), cardiovascular (patent ductus arteriosus), metabolic (hyperkalemia) (28).

Drug hypersensitivity reactions with macrolides occur in 0.4-3%. Commonly, skin manifestations are being reported. Mostly seen immediate reactions are urticaria, angioedema and rarely anaphylaxis. Non-immediate reactions are commonly maculopapular rash, exfolative dermatitis, urticaria, erythema, abdominal pain and respiratory symptoms. Although skin tests are not validated enough for macrolides, the combination of skin tests and provocation test to the culprit drug may lead to confirmantion of macrolide allergy (29).

ANTIVIRAL THERAPY

Lopinavir/ritonavir

Lopinavir/ritonavir is HIV protease inhibitor. In the past, it was used in MERS-CoV and SARS-CoV treatment. It may bind a key enzyme for coronavirus replication and supress the activity (10). The safety, efficacy and pharmacokinetic profiles of lopinavir and ritonavir should not be used in newborns younger than 14 days (8). It is contraindicated in liver failure and in heart diseases (ischemic heart disease, cardiomyopathy, long QT). Drug drug interactions are frequent because the P 450 isoform is a CYP3A inhibitor (10). The adverse events in adults who were using lopinavir/ritonavir for HIV disease, are commonly diarrhea (also other gastrointestinal disturbances), headache and skin rash. In children skin rash is the most common adverse event and severe reaction is rare. Also hypercholesterolemia and hypertriglyceridemia are seen commonly (30). It can lead to prolonged cardiac conduction defects and QT interval, 2nd and 3rd degree AV block (30). In a recently published study about the use of lopinavir/ritonavir in Covid 19 patients, there was no significant difference of adverse drug effects in liver toxicity and side effects between control and patient group (31).

Favipiravir

Favipiravir is a purine nucleic acid analog that is used for influenza and Ebola in the past. In clinical trials, it showed a significant reduction of viral RNA load and increment in clinical improvoment in coronavirus patients (32).

The adverse reactions are commonly diarrhea, an asymptomatic increase of blood uric acid and transaminases, and a decrease in the neutrophil counts. Some studies showed that favipiravir affects the hepatic drug metabolizing enzymes and causes acetominophen level to increase. When combined with favipiravir, the recommended maximum daily doses of acetaminophen are 3g (32). In a recently published study of Covid 19 patients who were treated with favipiravir or lopinavir/ritonavir treatment, side effects were significantly lower in favipiravir treatment group. Diarrhea was the most common side effect in Covid 19 patients who were treated with favipiravir (33).

Oseltamivir

Oseltamivir is a neuaraminidase inhibitor that is commonly used in influenza. The most frequently reported adverse events are nausea, diarrhea, vomiting and headhache (34). Rare adverse events include serious skin reactions, cardiac arrhythmias, and neuropsychiatric episodes. The neuropsychiatric side effects included delirium, suicidal events, panic attacks, delusions and

disturbances in consciousness (35). No studies showing the side effect of oseltamivir treatment in coronavirus have been reported yet.

Biological Agents

During the COVID-19 infection, it was observed that the macrophage activation syndrome (MAS) could develop, with or without signs of sepsis and ARDS, and these patients were reported to benefit from anti-cytokine treatments. Based on a few patient studies, tosilizumab and anakinra has been reported to have a positive effect on COVID-19-associated MAS. The efficacy of tocilizumab, other IL-6 blocker and IL-1 blocker anakinra drug in serious course COVID-19 disease is being investigated by controlled clinical studies (8).

Hypersensitivity reactions to biologic agents have been classified as infusion-related reactions, cytokine-release reactions, type I (IgE/non-IgE), type III, and delayed type IV reac- tions (36). The infusion-related and cytokine-release reactions include fever, tachycardia, hypertension, dyspnea, nausea, vomiting, and syncope that commonly occurs at first application (36).

Tosilizumab

Tosilizumab is an IL-6 receptor inhibitor monoclonal antibody. Indicated for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular (>2 years) and systemic (>2 years) juvenile idiopathic arthritis and cytokine release syndrome (10).

The risk of gastrointestinal perforation and hepatotoxicity is important in using tosilizumab. It should be used with caution in patients with thrombocytopenia and neutropenia (10).

There infusion related reactions may be seen (10). The infusion related reactions includes fever, tachycardia, hypertension, dyspnea, nausea, vomiting, and syncope and commonly happens at first administration. There have been published children cases who had anaphylaxis with tosilizumab treatment (36).

Anakinra

Anakinra is an IL-1 receptor antibody. The most common adverse effcet is a local reaction at injection site (37). A case who had anaphylaxis with anakinra, continued treatment with canakinumab desensitizastion was reported (38).

CONCLUSION

Besides adverse drug effects and drug-drug interactions, hypersensitivity reactions may develop with drugs used during Covid-19 therapy. Physician should be careful in this regard during the follow-up of Covid-19 patients. In case of drug hypersensitivity reaction; discontinuing of the drug, treatment of the developing reaction and making an appropriate and safe treatment plan for the disease are important.

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Management of Trauma And Surgical Procedures in Children During The COVID-19 Pandemic

COVID-19 Pandemisinde Çocuklarda Travma ve Cerrahi Prosedürlerin Yönetimi

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ABSTRACT

Coronavirus 2019 (COVID-19) infection was first identified in China and spread to the whole world in a very short time. The COVID-19 pandemic was declared by the World Health Organization (WHO) in March 2020 due to the rapid increase in the number of cases and deaths. Studies show that the virus is primarily transmitted by respiratory droplets and close contact. Although 90% of children are asymptomatic or have mild symptoms, they should be accepted as positive until they are proven negative regardless of any complaints. Despite the process, trauma, burn and surgical emergencies continue to concern pediatric surgeons. The basic principles those generally accepted during Covid-19 pandemic are to perform emergency and urgent surgical procedures and to reschedule elective surgeries. However, the most important issue in the process is to take precautions for protecting the healthcare team and to plan keeping hospital reserves. We aimed to adapt general principles of trauma and surgery to the COVID-19 pandemic in children and to discuss the specific conditions in our review.

Key Words: COVID-19, Pandemic, Pediatric surgery, Surgical procedures, Trauma

ÖZ

Coronavirus 2019 (COVID-19) enfeksiyonu ilk olarak Çin'de tanımlanmış olup tüm dünyaya kısa sürede yayılmıştır. Vaka ve ölüm sayılarındaki hızlı artış nedeniyle Mart 2020'de Dünya Sağlık Örgütü (WHO) tarafından COVID-19 pandemi ilan edilmiştir. Çalışmalar virüsün özellikle solunum damlacıkları ve yakın temas yoluyla yayıldığını göstermektedir. Çocuklarda hastalık %90 oranında asemptomatik veya hafif seyirli olmasından dolayı her olguya yakınması olmasa bile aksi ispat edilinceye kadar pozitif gibi yaklaşılmalıdır. Sürece rağmen travma, yanık ve cerrahi aciller çocuk cerrahlarını meşgul etmeye devam etmektedir. Pandemi esnasında, acil ve ertelenemeyen cerrahi işlemlerin yapılması, elektif cerrahilerin ertelenme prensibi benimsenmiştir. Ancak süreçte önemli olan, travma sonrası izlemde ve/ veya cerrahi işlemler esnasında olası bulaş riskinden dolayı sağlık ekibini korumaya yönelik önlemlerin tam alınması ve hastane şartlarının doğru planlanmasıdır. Derlememizde, çocuklarda mevcut travmaya yaklaşımın ve cerrahi prensiplerin COVID-19 pandemi sürecine uyarlanması, ortaya çıkan özellikli durumların tartışılması amaçlanmıştır.

Anahtar Kelimeler: COVID-19, Pandemi, Çocuk cerrahisi, Cerrahi girişimler, Travma

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INTRODUCTION

Severe acute respiratory coronavirus 2 (SARS-CoV-2) and also named as Coronavirus Disease 2019 (COVID-19) was first described in December 2019. Although Wuhan, China was the first place where the disease was seen, it spread to whole world in a very short time and was declared as a pandemic by the World Health Organization (WHO) in March 2020 (1). According to the Centers for Disease Control and Prevention (CDC) data on April 2020, there were approximately 900.000 cases and 45.000 death cases related with Covid-19, and the number of deaths are still reaching around 320.000 by the end of May, 2020. It is remarkable that 22% of all cases in America are infants, preschool children and adolescents (2, 3).

Surgical emergencies continue to concern the pediatric surgeons and they also have to deal with trauma and burn which are likely candidates for surgery. Despite the pandemic, main principle remains to provide timely surgical care. However, treatment plans should be revised by taking preventive measures for the healthcare team, who has close contact with the patients. It is recommended to question the patients about the presence of complaints or symptoms with the laboratory diagnosis of COVID-19 is based on a positive rRT-PCR (reverse transcription polymerase chain reaction) ideally. But tests can be false negative in the incubation period and their predictive value may not represent accurate results. Epidemiological and clinical data should be evaluated together (4). All the traumas and surgical patients should be managed with the following details.

Laboratory Diagnosis of Covid-19 is Based on A Positive Rt-Pcr

A. Epidemiological data

1. Does the patient live or come from a COVID-19 affected region in the last 14 days?
2. Did the patient have any close contact with COVID-19 during the last two weeks?
3. Are there any complaints of fever and/ or cough during the last two weeks?

B. Clinical / Radiological / Laboratory data

1. Are there of fever and/ or respiratory symptoms?
2. Is there any imaging characteristics of COVID-19?
3. Do the patient's blood tests reveal a reduced level of white blood cell (WBC) count or lymphocytes.

Accordingly, if there are one epidemiological and two or three clinical data, the patient should be considered as COVID-19 suspected/ positive regardless of the presence of epidemiological data (4).

General Principles For Medical Centers

A patient entering emergency department should be evaluated for the presence of specific symptoms or complaints of COVID-19 initially. At the same time, the urgency of patient's condition and requirement of intensive care must be determined. The patient should be isolated from other patients in the presence of high-suspicion. A dedicated imaging room (X ray, CT) should be arranged for these patients, and a predetermined transport route minimizes exposure. Personal protective equipment and medical masks have to be worn by both the patient and healthcare team.

Organizing the use of intensive care unit (ICU) may help keeping hospital reserves. Isolated area is recommended in the ICU and the treatment should be provided in a single area for the patients with suspected or confirmed COVID-19.

A three-level precaution protocol is defined to standardize measures. When a trauma patient is admitted to the emergency service, the assessment should be done according to the above criteria. But, it should be noted that the incubation period of COVID-19 may last up to 24 days. Therefore, even if there is no epidemiological or clinical finding, it is recommended to apply level 1 measures. Level 2 / Level 3 protective protocols should be used in the patients with suspected/ positive epidemiological and clinical data.

Level 1 precautions should be used in triage and at emergency room. The healthcare professionals have to use clean, non-sterile long gown, a disposable head cover, medical mask and gloves.

Level 2 should be applied at the presence of close contact with suspected patients, or exposure to blood or other body fluids/substances. Head cover, gloves, N95 respirator or equivalent, and rubber boots are included at level 2. In addition, all dressings should be done with level 2 protective equipment in burn cases.

Level 3 precautions are necessary for close contact with suspected patients, exposure to blood, respiratory tract samples like endotracheal intubation. Also, emergency surgery is another situation that level 3 measures must be applied. Measures should be strengthened compared to level 2. Wearing secondary protective equipment such as face shield, two layers of gloves/ protective overalls are included at level 3.

Surgical Interventions

The surgical procedures are categorized into three groups by the American College of Surgeons. The classifications are done according to the urgency of interventions. The main principles are to protect healthcare workers and hospital resources as shown below (5).

A Emergency situations (life threatening if delayed).

B Urgent cases (harmful for the patient within days or weeks if postponed).

C Elective cases (delaying brings minimal risk to the patient.)

The basic principles, among those generally accepted during Covid-19 pandemic are to perform emergency and urgent surgical procedures and to reschedule elective surgeries. Recent reports showed that the virus is primarily transmitted through respiratory droplets and close contact. Based on the fact that the disease is 90% asymptomatic, or moderate in children, consideration should be given to the possibility of viral contamination in each patient. It is strongly recommended to take preventive measures for considering the risk of inflow by droplet. The procedures should be planned by prioritizing personnel safety. When we apply pediatric surgery practices to the Covid-19 pandemic, the important points are summarized below as items.

a Timing for surgery

- "Emergency situations" are identified as the cases that any delay can be life-threatening. Acute intestinal obstruction, traumas, burns, appendectomy for acute appendicitis, most of congenital anomalies of newborn and foreign body aspirations can be evaluated in this status. The recommendation for the emergency cases is to perform surgery immediately without ignoring the protection of health workers. Interesting details related with Covid-19 in neonates (5). Although no findings of SARS-CoV-2 were found in newborns born from affected mothers, a recent study suggested that vertical maternal-fetal transmission can be a possibility. Therefore, Covid-19 positivity should not be kept in mind for neonates who undergo for neonatal surgery (6).
- The cases like most of the oncologic surgeries, portoenterostomy for biliary atresia, vascular access device insertion and symptomatic inguinal hernias can be evaluated in "urgent cases". More than a few days or weeks of delay can be harmful for these groups of patients. The most preferred approach is performing surgery immediately after the appropriate conditions should be provided.
- "Elective cases" cause minimal risk for the patient due to delay. Most of outpatient surgical procedures like asymptomatic inguinal hernia and anorectal malformation or Hirschsprung Disease reconstructions following diversion can be given as examples for elective cases. The surgical care should be limited to those which may be harmful to the patient due to any delay.

b Securing healthcare workers

Although patients undergo preliminary assessment for the possibility of COVID-19, surgical procedure of asymptomatic patient can risk the healthcare team. The procedures should be planned with the goal of securing healthcare workers.

c Selection of surgical procedures

There is little evidence to suggest/against the open and laparoscopic approach; however, the surgical team should choose an approach that minimizes OR (operation room) time and maximizes safety for both patients and healthcare professionals (5). The risk of viral contamination is a serious entity whether it is related to laparoscopic or open surgery. The general principle is that all operations should be performed quickly and effectively in order to reduce contact (8).

The American Gastrointestinal and Endoscopic Surgeons Association (SAGES) and European Association for Endoscopic Surgery (EAES)'s "Surgical response to COVID-19 crisis" recommendations are essential if needed (9).

d Management of Operating Room

- An operating room (OR) should be identified for all confirmed or suspected cases of COVID-19. The OR should have negative atmospheric pressures. -10 /-5 pKa pressure is recommended.
- The use of humidification system is not recommended in the operating room. The aspiration system should not be connected with the main system.
- When the patient is placed on the operating room table, the negative pressure aspirator should be placed in the patient's mouth and nose area to prevent secretions from spreading into the room.
- It is recommended to apply level 3 measures for emergency surgeries.
- Aerosol-producing procedures (AGPs) should be an important risk for the healthcare team, but cannot be prevented. AGPs have to be performed when full PPE is worn, including an N95 mask. Intubation, extubation and bag masking can be listed in AGPs. This is a serious risk for the medical team and the anesthesia team who are using the same operating room. Moreover, procedures like bronchoscopy and chest tubes are included in the AGPs, and pediatric surgeons should be careful when doing these surgical procedures. AGPs, are listed below.

a Bronchoscopy, chest tubes

b Blood electrocautery, contact to any gastrointestinal tissue, or body fluids

c Laparoscopy / endoscopy

For minimal invasive surgery (MIS), incisions for the ports should be kept as small as for the guidance of intervention, but not allow for leakage. CO2 insufflation should be kept to minimum and CO2 should be evacuated totally after the procedure. Care should be taken about the virus that can survive in aerosols for hours and on surfaces for days (10).

Although it is recommended to postpone elective cases as much as possible in the COVID-19 pandemic, the feature that distinguishes pediatric surgery from many other branches is that there are many causes of emergency surgery. In addition to trauma, many surgeries that cannot be postponed require urgent intervention. Therefore, in cases where surgery is unavoidable, appropriate protective measures should be the most important issue to ensure the safety of the personnel.

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COVID-19 Sürecinde Sağlık Sistemlerinin Zorlukların Üstesinden Gelebilme Kapasitesinin Geliştirilmesi ve Hemşireler ile Diğer Sağlık Profesyonellerinin Güçlendirilmesi

Enhancing the Capacity of Health Systems to Overcome Challenges and Strengthening Nurses and other Healthcare Professionals in COVID-19 Process

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ÖZ

Günümüzde, lider ve yöneticiler tam anlamıyla çözümü olmayan, kariyerlerini ve kurumlarının geleceğini tehdit eden, tarafların zarar görmesi kaçınılmaz karmaşık birtakım problemlerle karşı karşıya kalmaktadırlar. Birbiriyle çelişen belirsiz bilgileri değerlendirirken yönetici ve liderin önceliği çoğunluğa en az zarar veren çözümü uygulamaya koymak olması gerekmektedir. COVID-19 gibi pandemiye neden olan ve yaşantılarımızı belirsizliğin hakimiyetine bırakan bir süreç eklenince hem kişisel hem de sağlık meslekleri olarak yönetmemiz gereken birden fazla kriz durumu ortaya çıkmıştır. Burada önemli olan husus, Quantum çağında karşılaştığımız bu olağanüstü durumları nasıl yönettiğimiz ve bu sürece nasıl liderlik ettiğimiz ile ilişkilidir.

Bu planlama sürecinde değişime nasıl ayak uyduracağımız ve nasıl liderlik edeceğimiz önemli bir konudur. Çünkü insanlar en önemli insan hakkı ve anayasal hakkı olan "yaşama hakkı" bağlamında bir riskle karşı karşıya kalmışlardır. Bu nedenle de bu süreçte kendimizi nasıl koruyacağımız ve nasıl sağlıklı kalacağımız en önemli önceliklerimiz olmuştur. Sağlığın korunması ve güçlendirilmesi denince akla ilk gelen hiç kuşkusuz bu konuyu kendisine mesleki ilke edinmiş olan sağlık profesyonelleridir. Sağlık profesyonellerine bu kriz yönetiminde, planlama, hız, uyum ve güven oluşturma açısından önemli sorumluluklar düşmektedir. Derleme tarzında hazırlanmış bu makalede COVID-19 sürecinde, yönetici ve liderlerin içinde bulundukları sağlık sisteminde zorlukların üstesinde gelebilme kapasitelerinin geliştirilmesi ile hemşirelerin ve sağlık profesyonellerinin güçlendirilmesi kapsamında yapılabilecekler tartışılmıştır.

Anahtar Sözcükler: Covid-19, Hemşireler, Güçlendirme, Liderlik, Yönetim

ABSTRACT

Nowadays, leaders and executives are faced with a complex set of problems that do not have a complete solution, threaten their career and the future of their institutions, and that the parties are harmed. When evaluating ambiguous information that contradicts each other, the priority of the manager and leader should be to implement the solution that gives the least harm to the majority. When a process such as COVID-19, which caused a pandemic and left our lives under uncertainty, more than one crisis situation emerged, which we had to manage both personally and as healthcare professionals. The important point here is related to how we manage and lead these extraordinary situations we encountered in the Quantum era.

How we keep pace with change and how we can lead this planning process is an important issue. Because people faced a risk in the context of the most important human right and constitutional right "right to live". Therefore, how to protect ourselves and stay healthy during this process have been our top priorities. The first thing that comes to mind when it comes to protecting and strengthening health is undoubtedly the health professionals who have adopted this

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issue as a professional principle. Health professionals have important responsibilities in planning this crisis in terms of planning, speed, compliance and trust. This article, prepared in a compilation style, discusses what can be done within the scope of the COVID-19 process, by improving the capacity of managers and leaders to overcome difficulties in the health system they are in and strengthening nurses and health professionals.

Key Words: Covid-19, Nurses, Empowerment, Leadership, Management

GİRİŞ

İnsanoğlu yeryüzünde var olduğu ilk yıllardan itibaren, doğal çevredeki olayların dışında her gün kendi yarattığı sürekli bir değişimi yaşamaktadır. Değişimin hızı asırlarla değil, saatlerle hatta dakikalarla ölçülür hale gelmiştir. Dünyanın neresinde olursanız olun, sağlık ve sağlık ihtiyaçlarının karşılanması, toplumsal kaygıların ve tartışmaların odak noktasıdır. Hatta sağlıkla ilgili durumlar, çoğu zaman haberlere konu olabilmektedir. Bu durum, bazıları tahmin edilebilir, bazıları ise tahmin edilemez birkaç sebepten kaynaklanabilir ve global sağlık sistemlerinin kırılganlığı anlaşılmıştır. Aynı derecede diğer bir zorluk ise, pandemiye neden olan küresel sağlık krizleri ile karşı karşıya kalınmasıdır. Dünya Sağlık Örgütü (DSÖ)'ne göre pandemi olabilmesi için gerekli kriterler; toplumda daha önce görülmemiş bir hastalığın ortaya çıkması, hastalığın etkeni olan patojenin insanlara bulaşarak tehlikeli bir hastalığa yol açması ve hastalık etkeni patojenin insanlar arasında kolayca ve devamlı olarak yayılması yani bulaşıcı olmasıdır. Bir hastalığın pandemi olarak ilan edilebilmesi için istikrarlı bir şekilde, dünyanın farklı noktalarında, kitleler üzerinde görülmeye başlaması gerekmektedir ve DSÖ tarafından ilan edilir. Dünyada ilk pandemi nedeniyle karantina uygulanması 1377 yılında Dubrovnik ve Venedik'de cüzzam salgını nedeniyle olmuş ardından 300 yıl sonra ise İngiltere'de veba salgını ile devam etmiştir. Pandemi tarihine baktığımızda bugüne kadar insanlığı etkileyen 21 pandemi meydana geldiğini, çok sayıda insanın ölümü ile sonuçlandığı ve dünyayı en çok etkileyen salgınlar arasında cüzzam, veba, kolera, grip, AIDS, SARS, Ebola ve günümüzde de COVID19 olarak gündeme gelmiştir. Bunlar içerisinde 2014'te Batı Afrika'da ortaya çıkan Ebola salgını, sağlığın korunması için global düzeyde ülkelerin harekete geçebilmesinin önemini göstermiştir. Enfeksiyonlarda, aynı insanlar gibi sınırları aşabilmekte ve dünyanın her bir köşesine yolculuk etmekte; doğal felaketler ve çatışmalar ülke sınırı tanımamakta ve dünyadaki tüm ülkelerin sağlığını etkilemektedir. Dünya sağlığını etkileyen virüslere yönelik ortaya çıkan salgınlar ülkeler arasında hızlıca yayılabiliyor; hızlı ve etkin şekilde müdahale yeteneğine sahip bir sağlık sistemi yoksa çok büyük sorunlara yol açabiliyor (1,2).

Coronavirusler, Corona viridae familyasına ait olan ve hem hayvanları hem de insanları enfekte eden bir virüs grubudur. Coronaviruslerin bazı türleri insanlarda soğuk algınlığına benzer hafif hastalıklara neden olurken, diğer türleri (MERS - Orta Doğu Solunum Sendromu ve SARS - Şiddetli Akut Solunum Sendromu gibi) daha ciddi hastalıklara neden olabilmektedir. Daha önce insanlarda görülmemiş olan yeni bir coronavirus türü olan ve kısaca COVID-19 olarak adlandırılan coronavirus hastalığı ise Aralık 2019'da Çin'in Wuhan şehrinde ortaya çıkmıştır. Belirti ve bulguları arasında; başlangıç döneminde ateş, öksürük ve nefes darlığı, daha ciddi vakalarda ise pnömoni, ciddi akut solunum sendromu ve bazen de ölüm görülür (3). Günümüzde ortaya çıkan bu COVID-19 pandemisinden en çok etkilenen ülkelerde gördüğümüz manzara, yetersiz sayıda sağlık çalışanına ve sağlık ekipmanlarına sahip sağlık sistemleri son derece kırılgan bir yapıya sahip olduğudur. Müdahalelerin zamanında yapılmaması, mevcut sağlık hizmetlerinin çökmesine, salgından etkilenen insanların tedavisinden sorumlu sağlık hizmeti çalışanlarının hayatını kaybetmesine ve dolayısı ile de toplum sağlığının daha büyük tehditlere maruz kalabilmesine neden olmaktadır. Dünya Sağlık Örgütü (4). Ebola'dan etkilenen sağlık çalışanlarının %50'sinden fazlasının hemşire ve hemşire yardımcısı olduğu ve virüsten etkilenen sağlık çalışanlarının üçte ikisinin hayatını kaybettiği belirtmiştir (5,6).

COVID 19 sürecinde de pek çok sağlık çalışanının hem kendisi hem de aile ve yakınları etkilenmiş, hayatını kaybetmiş ve etkilenmeye de devam etmektedir. Sağlık çalışanlarının COVID-19 enfeksiyonundan etkin şekilde korunabilmeleri için, etkeni iyi tanımaları, nasıl, nerede, ne şekilde bulaş riskinin arttığını bilmeleri ve uygulamaları gereken korunma önlemlerinin farkında olmaları gereklidir. Sınırlı sayıda yayın sağlık çalışanları arasındaki enfeksiyon için risk faktörleri belirlemiştir. Ön sonuçlar, sağlık çalışanlarının hem işyerinde hem de toplumda, çoğunlukla enfekte aile üyeleri aracılığıyla virüsü aldıklarını göstermektedir (7). 10 Nisan 2020 tarihli bir durum raporunda, 15.334 sağlık çalışanının hastalığa yakalandığı, bu sayının toplam vaka sayısının %11'ini oluşturduğu belirtilmiştir (8). Sağlık çalışanlarında COVID-19 enfeksiyonunun görülmesi ile ilişkili olarak hastalarda COVID-19 tanısının erken dönemde konamaması, yüksek riskli bir bölümde çalışma, uzun çalışma saatleri, uygun olmayan el hijyeni uygulamaları gibi enfeksiyon önleme ve kontrol önlemlerine yeterli düzeyde uyulmaması ve kişisel koruyucu donanımların (KKD) eksikliği veya uygunsuz kullanımı gibi faktörler üzerinde durulmaktadır (9,10). COVID-19 virüsü dahil solunum patojenleri için eksik veya yetersiz enfeksiyon önleme ve kontrol eğitimi ve çok sayıda COVID-19 hastasının bakımının yapıldığı alanlarda uzun süre zaman geçirme gibi başka faktörler de bildirilmiştir. COVID-19 hastalarının bakımında ve tedavisinde görev alan sağlık çalışanları, normalden daha uzun süre çalıştıkları, kendi aile üyelerine hastalığı bulaştırma endişesi ile onlardan uzak kaldıkları, yoruldukları, tükendikleri, damgalanmaya, fiziksel ve psikolojik şiddete maruz kaldıkları için, onların fiziksel ve zihinsel sağlığının korunması ve sürdürülmesi için çaba sarf edilmesi önemlidir. Bu nedenle DSÖ, tükenmişlik riskinin azaltılması, güvenli ve sağlıklı çalışma ortamlarının oluşturulması ve sağlık çalışanlarının iyi çalışma koşullarında istihdam edilme haklarına

saygı duyulması için enfeksiyon önleme ve kontrol önlemlerinin, iş sağlığı ve güvenliği önlemlerinin alınmasını ve psiko-sosyal desteğin, yeterli nitelik ve nicelikte personelin istihdam edilmesini ve klinik rotasyon yönteminin uygulanmasını önermektedir (11).

Bu salgın birçok soru işaretini de beraberinde getirmiştir. Hastalıktan veya ölümden kaynaklanan sağlık hizmeti çalışanı eksikliğine nasıl hızlı şekilde müdahale edilebilir? Hemşire ve diğer sağlık profesyonelini iş gücünü farklı alanlarda hizmet verebilmeleri için nasıl çabucak eğitebiliriz? Doğru ekipmana hızlı şekilde nasıl ulaşabiliriz? Toplum ile etkin şekilde nasıl iletişime geçebiliriz? Bu tarz krizlere zamanında ve etkin şekilde müdahale edebilirken aynı zamanda da gerekli temel sağlık hizmetlerini sağlamaya devam eden sağlık sistemlerine ihtiyacımız olduğu ortadır. Bir sağlık sisteminin zorlukların üstesinden gelebilme kapasitesi, çatışma, doğal afet ve bir hastalığın aniden yayılması gibi kriz durumlarına maruz kalındığında cevap verebilme, uyum sağlayabilme ve güçlenebilme kapasitesine bağlıdır (12, 13). Sağlık sisteminin zorlukların üstesinden gelme kapasitesi, sağlık sistemi öznelerinin, kurumların ve ülke nüfusunun ,krizlere verimli şekilde tepki verebilmesi ve bunlara hazır olması, krizle karşılaşıldığında sistemin ana fonksiyonlarını devam ettirebilmesi, kriz sırasında öğrenilenlerden ders çıkarabilmesi ve eğer koşullar gerektiriyorsa baştan organize edilebilmeleri anlamına gelmektedir (14,15).

"Küresel Sağlık 2035: Tek kuşakta birleşen Dünya" isimli Lancet Komisyon raporunda, sağlığa yapılan yatırımların ne kadar önemli olduğu belirtilmektedir. Rapor, sağlık teknolojilerinin seviyesini yükseltecek ve dağıtım sistemlerini iyileştirecek gelişmiş yatırımlar ile anne-çocuk ölüm oranlarının yanı sıra bulaşıcı hastalıklardan kaynaklanan ölüm oranlarının da evrensel düzeyde düşük seviyelere çekilebileceğini gösteren ayrıntılı bir analiz sunmaktadır. "Birleşmenin sağlanması durumunda 2035'te alt ve alt-orta gelir seviyesindeki ülkelerde 10 milyona yakın ölümü önlenebileceği öngörülmektedir (16).

Zorlukların derecesi ne olursa olsun, herkese her yaşta sağlıklı yaşam ve iyi olma durumu sağlamaya odaklanmanın sürdürülebilir gelişmenin esaslarından olduğu, günümüzde küresel düzeyde kabul görmektedir. Güçlü, zorlukların üstesinden gelebilen ve hızlı değişimlere anında cevap verebilen sağlık sistemlerine olan ihtiyaç, Birleşmiş Milletler Sürdürülebilir Kalkınma Hedefleri (SKH'ler)'nin tam kalbinde yer almaktadır. SKH Hedef 3'de, her yaştan herkese sağlıklı yaşam sağlamak ve sağlıklı olmayı teşvik etmek, diğer sürdürülebilir kalkınma hedeflerine ulaşmanın temelini oluşturuyor. Evrensel Sağlık Güvencesi sadece ihtiyacı olanlara sağlık hizmetlerini ulaştırmayı değil, insan merkezli kaliteli sağlık hizmetlerinin sunulmasını amaçlıyor. Bu, yeterli sayıda iyi eğitilmiş ve istekli sağlık çalışanına sahip iyi işleyen bir sağlık sistemini gerektirmektedir. 2030'da yaklaşık 10.1 milyon sağlık çalışanı (hemşireler, ebeler, hekim) açığı olacağı öngörülmektedir (17). Binyıl Kalkınma Hedefleri'ne ulaşmada zorluk yaşayan ülkelerin çoğu, sağlık iş gücü eksikliği ve bu iş gücünün yanlış dağıtımından muzdarip olmaktadır. Hemşirelerin de dahil olduğu kalifiye sağlık personelinin azlığı, etkin sağlık sistemine ulaşmadaki en büyük engellerden biri olarak görülmektedir (18).

Bu nedenle, Dünya Sağlık Örgütü, Sağlık'ta İnsan Kaynakları üzerine Küresel Strateji (HRH): İş Gücü 2030'u geliştirmiştir. Tüm sağlık çalışanlarının, güvenli ve insancıl yaşam koşullarına sahip olmaları ve her türlü baskı ve şiddetten korunması gerektiği vurgulanmıştır. Sağlık sistemlerini güçlendirmede ve bunların zorlukların üstesinden gelme kapasitelerinin arttırılmasında toplumsal sağlığın rolünün tüm hemşireler ve diğer sağlık çalışanları için bir öncelik olduğu açıktır. Sağlığın geliştirilmesine, hastalık ve rahatsızlıkların önlenmesine yatırım yapılması; kişilerin sağlıksız duruma geçmeleri ile sağlık sistemi üzerinde yaratacakları talebi ortadan kaldırarak ve sağlıklı ve üretken kalan vatandaşların topluma yapacakları ekonomik katkı ile pozitif bir etki yaratabilir (16,19). Sürdürülebilir Kalkınma Hedefleri ve Sağlıkta İnsan kaynakları önerilerinde yer alan, karar almaya dair bütün tavsiyeler, sağlığın sosyal belirleyenleri üzerinde yapılacak çalışmaların, uzun vadede klinik sonuçları iyileştirmesi, para ve zaman tasarrufu sağlaması sebebiyle, sağlık çalışanlarının işinin merkezi bir parçası olması gerektiğini söylüyor.

Günümüzde sağlık profesyonellerinin ve özellikle 24 saat kesintisiz hizmet veren hemşirelerin günlük uygulamalarında, güçlü sistemlerin oluşturulması yolunda ciddi bir role sahip oldukları açıktır. Sağlıklı yaşamı ve sağlıklı olmayı teşvik etmenin özünde bütün hemşireler için yatan temel prensip, sosyal adalet kavramıdır. Sosyal adalet kavramı sağlığa ve sağlık güvencesine uygulandığında, sağlık hizmetlerine erişimden daha fazlasına işaret ederek; ayrıca, barınma, gıda güvencesi, ulaşım, çalışabilme ve eğitime erişim anlamına da gelmektedir. Sosyal adalet için harekete geçmek, farklılıkları azaltmak ve eşit erişim imkânını yaymak anlamına gelir (20-22).

Dünya Sağlık Örgütü, 6 temel ilkeye tekabül eden 6 ana alanda uzun vadeli yatırım yapılmasını önermektedir.

1. Yeterli sayıda eğitilmiş sağlık çalışanı
2. İlaçlara ve gerekli tıbbi malzemelere ulaşabilme
3. Denetimleri ve izlemeyi de içeren güçlü sağlık bilgi sistemleri
4. Uygun altyapı oluşturma
5. Yeterli kamusal finansman
6. Eşit ve kaliteli hizmet sağlayacak güçlü bir kamu sektörü

Sonuç olarak, sağlık sisteminin zorlukların üstesinden gelme kapasitesi, sağlık sistemi öznelerinin, kurumların ve ülke nüfusunun krizlere verimli şekilde tepki verebilmesi ve bunlara hazır olması, krizle karşılaşıldığında sistemin fonksiyonlarını devam ettirebilmesi, kriz sırasında öğrenilenlerden ders çıkarabilmesi ve eğer koşullar gerektiriyorsa baştan organize edebilmeleri anlamına gelmektedir.

Sağlık Sistemlerinin COVID 19 Sürecinde Başarması Gereken Hedefler

Panter-Brick (23), "Sağlık söz konusu olduğunda, risk üzerine yapılan araştırmalar, zorlukların üstesinden gelebilme kapasitesi

üzerine yapılan araştırmalara göre genellikle baskın çıkığını ifade etmiştir. Ancak, sağlık araştırmaları ve uygulamalarında, dikkati riskten alıp zorlukların üstesinden gelebilme kapasitesine doğru çeken ve gittikçe büyüyen bir momentum söz konusudur (23).

Giderek artan bir şekilde kanıtlar, organizasyonun zorlukların üstesinden gelebilme kapasitesi ile organizasyonun çıktılarını birbirine bağlayan güçlü bir bağ olduğunu göstermektedir. Organizasyonun zorlukların üstesinden gelebilme kapasitesini geliştirmeyi destekleyen pozitif stratejiler içinde işten kaçınma ve işi başkasına yıkmanın azalması, sağlıklı olmanın gelişmesi ve üretkenliğin artması gibi çok önemli kişisel ve organizasyonel faydaları olan sonuçlar bulunmaktadır (24). Risk yönetimi, risklerin belirlenmesi, analiz edilmesi ve yönetilmesidir. Basit haliyle, hangi olayların (tehlikeler) gelecekte zarara yol açabileceğini belirlemek ve bu olayların gerçekleşme ihtimalini (Ne sıklıkta?) ve olası sonuçlarını (ne kadar kötü?) minimize etmektedir (25).

Başarılı sağlık sistemlerinin hedefi, uyum sağlayabilme, öğrenebilme ve esnek olabilmektir. Bu üç ana konsept, zorlukların üstesinden gelebilme kapasitesini oluşturma ve geliştirmede temel etkenlerdir.

- ***Esneklik;*** organizasyonun kolay bir şekilde işleyişini değiştirebilme yeteneğidir. İşleyiş ise; iş gücü istihdamı veya hizmet ulaştırma modelleridir.
- ***Uyum sağlayabilme***; bir organizasyonun belli durumlara uyum sağlayabilmesi veya belli bir amaç için daha iyi çalışabilmesi yeteneğidir.
- ***Öğrenebilme;*** öğrenebilen bir organizasyon üyelerinin öğrenme süreçlerini teşvik edebilen ve sürekli olarak kendini değiştirebilen organizasyondur

Kruk ve ark. (14), zorlukların üstesinden gelme kapasitesine sahip bir sağlık sisteminin 5 ana unsurunu tanımlamıştır:

1. ***Zorlukların üstesinden gelebilme kapasitesine sahip sistemlerde farkındalık vardır:*** Bu sistemler bilgiyi, risk ve müdahaleleri anlamak ve modellemek için kullanırlar
2. ***Zorlukların üstesinden gelebilme kapasitesine sahip sistemlerde kapsamlılık vardır:*** Ana sağlık hizmeti, iş gücü kapasitesi gibi birçok çeşitli kaynağı kullanarak geniş alana yayılmış zorlukları tespit edip, bunların üstüne gidebilirler.
3. ***Zorlukların üstesinden gelebilme kapasitesine sahip sistemler kendi kendilerini düzenler:*** Tehlikeleri tespit edip, onları izole edebilir ve bunu yaparken hala temel sağlık hizmetlerini sunabilir ve gerektiğinde ek kaynaklar oluşturabilir
4. ***Zorlukların üstesinden gelebilme kapasitesine sahip sistemler bütünleşik sistemlerdir:*** Temel ortaklar, topluluklar ve kurumlar ile güçlü bağlar kurarlar.
5. ***Zorlukların üstesinden gelebilme kapasitesine sahip sistemler uyum sağlayabilen sistemlerdir:*** Sadece kriz dönemlerinde değil, normal zamanlarda da demografik ihtiyaçlara göre, ülke içinde yer değiştiren insanlara ve hizmeti ulaştırma yöntemlerine göre kendilerini değiştirebilirler.

Tüm bunlar, zorlukların üstesinden gelebilme kapasitesine sahip sağlık sistemlerinin oluşturulması için ayrılmış sınırlı kaynakları nereye yatırmalı sorusunu gündeme getirmektedir. Unutulmamalıdır ki temel sağlık hizmeti, devletlerin ve toplumların karşılayabildiği maliyetlerde insanlara temel sağlık hizmetlerini ulaştırmanın verimli ve tercih edilen yoludur (26). Bir ulusal sağlık sistemi; insanlarına, bir dizi kamu tarafından fonlanmış, temel, herkes tarafından ulaşılabilir ve adil sağlık hizmetleri sunan bir temel sağlık hizmeti üzerine kurulduğunda, daha verimli hale gelmektedir (27). Finansman mekanizmaları yoksul insanların üzerinde ağır bir yük bindirmeden sağlık hizmetine herkesin ulaşabilmesini sağlamalıdır. Bu ise kaliteli sağlık hizmetine ulaşmanın önündeki, direkt cepten ödeme, sağlık kuruluşuna ulaşmada kat edilen fiziksel mesafe ve harcanan zaman gibi sağlık hizmetine ulaşmayı engelleyen bariyerleri ortadan kaldıran etkili bir finansman modeli gerektiriyor (28).

COVID 19 gibi bulaşıcı hastalıkların patlak vermesine etkili bir şekilde müdahale edebilmek için zorlukların üstesinden gelebilen sağlık sistemlerine, -uyumlu, bilinçli ve bütünleşik sistemlere- ihtiyacı vardır. Zorlukların üstesinden gelebilen sağlık sistemlerine yapılan yatırım küresel kamu yararı ve herkesin ortak çıkarı için yapılmış bir yardım olarak görülmelidir (11). Zorlukların üstesinden gelebilme kapasitesini geliştirmeye dair CIPD'nin hazırladığı rehber, bireylerin zorlukların üstesinden gelebilme yeteneği geliştirebilmeleri için uygulayabilecekleri üç yaklaşımı tanımlamıştır. Bu yaklaşımlar, odaklandıkları yere,- bireyin kendi niteliklerine, sosyal çevresine ya da her ikisinin birleşimine- göre belli başlıklarda toplanabilir (29):

1. ***Kişilik/Bireysel Nitelikler:*** Zorlukların üstesinden gelebilme yeteneği kişiye özeldir ve bireyin kişiliğinin bir parçasını oluşturan içsel bir yetenek olarak görülür. Ve bu kontrolün bireyde edindiği yeri (kişinin hayatı üzerindeki kontrolü), kişinin tahammül sınırını, duygularına dair farkındalığını ve bunları yönetimini, iyimserliğini, perspektifini, espri anlayışını, öz yeterliliğini (kişinin becerilerine olan inancı), ve problem çözebilme yeteneğini içerebilir.
2. ***Çevre:*** Zorlukların üzerinden gelebilme yeteneği tamamen kişinin çevresi ile girdiği etkileşimlere bağlıdır. Yani ne kadar sosyal destek aldığı gibi, kişinin elinde olmayan faktörler, kişinin zorlukların üstesinden gelebilme yeteneğinin seviyesini belirler. Bireyin kişiliği ise konuyla alakalı gözükmemektedir.
3. ***Kişi-Çevre:*** Zorlukların üstesinden gelebilme yeteneği; bireyin kişiliğinin, ailesi, yakınları ve sosyal çevresi gibi çevresel etkileyenler ile kombine edilmesinin bir ürünüdür.

Sull ve ark. (30) çalışanların iyiliğinin önemine ve hasta bakımındaki etkisine dayanarak, organizasyonların iş yerinde,

kişilere zorlukların üstesinden gelebilme yeteneğini öğreten girişimleri desteklemeleri için güçlü bir neden olduğunu belirtmektedir. İngiltere'de bulunan NHS Health and Wellbeing Review hasta bakımının etkinliği; hastaların deneyimleri, hasta güvenliği ve çalışanların sağlığı ve iyi olma durumları ile bağlantılı olduğu vurgulanmıştır (31). Bütün ulusal ve uluslararası sağlık organizasyonlarının gelecek için açık bir strateji ve vizyon geliştirmeleri gereklidir.

Zorlukların Üstesinden Gelebilme Yeteneği Üzerine Robertson Cooper Modeli (32; 33)

Küresel düzeyde pandemiye yol açan durumlarda, kişilerin bu süreçte zorlukların üstesinden gelebilmeleri için Robertson Cooper Modeli geliştirilmiştir. Bu model, COVID-19 sürecinde de kolaylıkla uygulanabilir.

Güven: Yetkinlik hissi, stresli durumlar ile mücadele etme etkinliği ve güçlü bir özgüven zorlukların üzerinden gelinebileceğinin hissedilmesinin özünde yer alır. Bireylerin ne aralıklarla pozitif ve negatif duygulara maruz kaldıkları da ayrıca önemlidir.

Amaç Sahibi olmak: Net bir amaç sahibi olma hissi, kişi için net olan değerlere sahip olmak, sahip oldukları istikamet ve yön kişilerin olumsuzluklar ile karşılaştıklarında mücadeleyi bırakmamalarını ve bunların üstesinden gelebilmelerini sağlamaktadır.

Sosyal destek Zorluklarla tek başlarına mücadele etmek yerine diğer insanlar ile iyi ilişkiler kurmak ve yardım istemek kişilerin olumsuz durumlardan daha kolay kurtulmalarını sağlar.

Uyum sağlayabilmek: Kendi elimizde olmayan durumlara uyum sağlamak ve esnek olabilmek zorlukların üstesinden gelebilme yeteneğine sahip olmada olmazsa olmazdır. Zorlukların üstesinden gelebilen bireyler değişiklikler ile daha iyi başa çıkarlar ve durumdan etkilenmeden önceki hallerine daha çabuk dönerler.

Refah uzmanları, Robertson Cooper'ın; kişinin zorlukların üstesinden gelebilme yeteneğini, yaşanılan tersliklerin etkili şekilde geride bırakılmasını da içeren, iş performanslarını ve iyi olma durumlarını baskı altında da devam ettirebilme kapasitesi olarak tanımlıyor. Bu uzmanlar, zorlukların üstesinden gelebilme yeteneğini güçlendirmede kullanılan eğitici ve geliştirici yaklaşımları desteklemekte kullanılan bir model hazırladılar. Kişinin başlangıç noktası ne olursa olsun zorlukların üstesinden gelebilme yeteneğinin pozitif şekilde geliştirilebileceği fikri de yine bu uzmanlara aittir.

Bu görüş ayrıca, Jackson ve ark. (34) yaptığı, sağlık profesyonellerinin özellikle de hemşirelerin zorlukların üstesinden gelebilme yeteneklerini geliştirerek ve güçlendirerek iş yerlerinde karşılaştıkları zorluklara olan kırılganlıklarını azaltabileceklerini öneren araştırma ile desteklenmiştir. Zorlukların üstesinden gelebilme yeteneği eğitimlerinin hemşirelik eğitiminde yer alması ve mentörlük programları aracılığı ile profesyonel desteğin sağlanması gittikçe artan şekilde önerilmektedir.

Sağlık Profesyonellerinin COVID 19 Sürecinde Zorlukların Üstesinden Gelebilme Yeteneğinin

Güçlendirilmesi: Sağlık profesyonellerinin zorlukların üstesinden gelebilme yeteneği ve sağlık hizmeti sağlayabilme yeteneği arasındaki ilişkinin anlaşılması önemlidir. Kriz durumlarında yaşanan toplumsal şokun kişiler arası şiddet ve intihar risklerini potansiyel olarak arttırdığını ve kişilerin refahı ve akıl sağlığı üzerinde anında etki gösterdiğini biliyoruz. İşsizlik akıl sağlığı için temel risk faktörlerinden biridir. Küresel düzeyde, üretkenliğin kaybolması, yılların işsizlikle geçmesi majör depresif bozuklukların en önemli ikinci nedenidir (35).

İyi bir çalışma ortamı, fiziksel ve akıl sağlığı açısından önemlidir. Çalışma ortamındaki bazı stres faktörleri ve yüksek beklenti seviyeleri çalışanları olumsuz olarak etkileyebilmektedir (34). Sağlık çalışanlarının işverenlerinin, sistemdeki en iyi uygulamaları modellemede liderlik rolünü üstlenmelerini bekleyebiliriz. Meslek uygulamalarındaki değişiklikler, yeniden yapılandırma ve sorumluluklardaki hızlı değişimleri; psikolojik stres, fiziksel tükenme, moral bozukluğu, çökkünlük hissi ve depresif bozuklukların görülme ihtimalini arttırabilir.

Sağlık profesyonellerinin ve hemşirelerin sağlık sistemlerini güçlendirmede ve zorlukların üstesinden gelebilme kapasitesini geliştirmede katkıları tartışılmazdır (36). Sağlık profesyonelleri içinde hemşirelerin dönüştürücü değişikliklerin lokomotifi oldukları birçok örnek bulunmaktadır; hemşireler, karar almadan uygulamaya kadar sistemin bütün kademelerinde birçok hizmetin insanlara ulaştırılmasındaki önemli aktivitelere liderlik etmektedirler. Bu nedenle sorumlulukları süreklilik arz etmektedir. Bu pandemi döneminde yeni beklentilere yönelik gerekli yeni yeteneklerini geliştirmeleri gereken üç öncelikli alan bulunmaktadır. Hemşireler ve diğer sağlık profesyonelleri etkilerini ve değişimin hızını arttırmak için; merkezde yer almalı, esnek, uyum sağlayabilen ve yeni öğrenme biçimlerine açık bireyler olmalıdırlar. Bu üç alan aşağıda belirtilmiştir:

1. Sağlık Profesyonelleri ve Hemşirelerin dijital teknolojilerin uygulanması ile ilgili rolü,
2. Kaliteyi ve etkiyi gösterebilme gücü
3. Sistem liderliği

1. Dijital Teknolojilerin Uygulanması

Dünya Sağlık Örgütü'nün açıkladığı güçlü bir sağlık sistemi için gerekli 6 temel ilkede bahsettiği üzere iyi çalışan bilgi sistemlerine ihtiyaç var ve bu hedefe ulaşmak için hemşireler uygun şekilde donatılmalılar. Sağlık hizmeti sistemleri ve iletişim teknolojilerinde gerçekleşen hızlı değişiklikler arasındaki bağlantı sağlık hizmeti yeniliklerinin daha önce hiç olmadığı kadar hızlı gelişmesini ve yayılmasını sağlamaktadır. Hemşireler, uzman danışmanlığının daha çok insana ulaşmasını sağlamak için teknolojiyi kullanarak uzak mesafelerdeki temel sağlık hizmeti ünitelerine bağlanabilmelidir. Günlük rutinlerinin içeriğinde hemşireler, teknolojiyi yaşamsal belirtileri gözlemlemek, ilaçları insana ulaştırmak ve sonuçları ölçmek için kullanmaktadır. Dijital

yöntemleri kullanmak, sağlık hizmetlerini ulaştırma şeklinin tamamen baştan ele alınması ve yeni fırsatların olduğu yerleri kavramaları gerekmektedir. Küresel düzeyde sağlık hizmetlerine her yıl 4 trilyon dolar harcıyoruz, ancak bunun çok az bir miktarı sağlık hizmetlerini dönüştürmek için digital teknolojiyi kullanılabilir hale getirmeye gidiyor. Elbette bu tek başına bir çözüm değil ve daha geniş bir değişim kültürü içine yedirilmediği sürece, etkisi de kayda değer olmayacaktır (37).

Hemşireler ve diğer sağlık profesyonelleri teknolojik sistemin liderleri olmalı ve teknolojinin, kaliteyi ve hasta güvenliğini geliştireceğini ve sağlık hizmeti yöntemlerini kökten değiştirebileceğini kabul eden bir anlayış geliştirmeli ve teşvik etmelidir. Dijital teknoloji, her klinik ortamda hemşireliğin ve diğer sağlık profesyonellerinin yer aldığı aşamaların her birisini etkilemektedir ve bu zorlu görevi üstlenecek liderlere sahip olunmalıdır. Cooper'ın belirttiği gibi "Teknolojiden ve bilgiden fayda sağlayabilmek, eğitimi, stratejik planlamayı ve çalışma şeklimizi geliştirmek için sağlık verilerinin iyi kullanılması gerekmektedir" (38).

Hemşirelerin bilgisayar ve bilgi teknolojilerine hazır oluş düzeyi hemşirelik bilişimi ve bilgi sistemlerinin gelişiminde önemli bir etmendir. Hemşireler hastanın gereksinimlerini belirleyerek, doğrudan bakım veren, verdiği bakımın sürekliliğini izleyen ve kayıt eden sağlık ekibinin önemli bir üyesi olarak sağlık bakım sisteminde önemi hızla artan teknolojinin en önemli kullanıcılarındandır. Hizmet ve uygulama alanlarında görev alan hemşirelerin bilgi gereksinimini fark etme, gereksinim duyulan bilgiye ulaşma, bu bilgiyi etkin kullanma, değerlendirme ve sunma olarak tanımlanan, bilgisayar okuryazarlığını da içine alan bilgi okuryazarlığı becerisine sahip olmasını gerektirmektedir.

2. **Kaliteyi ve Etkiyi Gösterebilme**

Sağlam bir bilgi altyapısı (yani dijital teknoloji) ikinci öncelik alanı için bir ön koşuldur. Hemşirelerin yaptıkları işlerin kalitesini ve etkilerini ne derece gösterebildikleri, sistemin geri kalanının hemşirelerin sahip olduğu rolü anlamasını ve buna değer vermesini sağlamada önemli bir noktadır. Kaliteyi ve etkiyi gösterebilmek, zorlukların üstesinden gelebilme kapasitesini geliştirmek adına ortaya koyulan hemşirelik katkılarının optimize edilmesi için gereken kaynakların ve çevrelerin harekete geçirilmesini sağlayacaktır (39). Hemşirelerin yaptıkları işler genellikle diğer insanlara görünmez gelir ve teknolojinin hizmetin eşiğinde kullanılması bu işlerin görünürlüğünü arttırabilir. Ancak, hemşirelerin kalite standartlarının geliştirilmesinde aktif şekilde yer almaları, karar alma ve sistem kademelerinin değişiklikleri üzerinde etkili olabilmek için daha geniş fırsatlara sahip olmaları birinci derece önemlidir. Bu durum kalite ve insan merkezleri sistemleri üzerine hemşirelik uzmanlığının etkisinin daha büyük olmasını sağlayacaktır. Hemşirelik uzmanlığı, hükümet ve karar alma mekanizmalarının her kademesinde görünür olmalı ve sağlık sistemi içinde kaliteli sağlık hizmetinin vatandaşlara ulaşmasında sahip olduğu önemli rol sebebiyle değer görmelidir.

3. **Sistem Liderliği**

Liderliğin doğası, hemşirelik ve sağlık hizmeti için önemi hakkında çok fazla şey yazılmıştır (40). Ancak daha önce tanımladığımız gibi; günümüzün hemşire liderleri, kendilerini atik ve esnek yöntemlerle çalışmaya zorlayan birçok öngörülen ve öngörülmeyen zorluk ve değişiklikle yüzleşmektedirler.

Hiyerarşik organizasyon yapısıyla bağlantılı olan tek bir organizasyonel modeli temel alan klasik liderlik modelleri sürdürülemez hale gelecektir. Özellikle kamu sektörlü liderliğinde; hizmetler bütünleşmiş oldukça, hizmet yöntemler dönüştükçe, kaynaklar paylaşıldıkça ve personel çok farklı yöntemler aracılığı ile görevlendirildikçe organizasyonel, mesleki ve coğrafi sınırlarda bulanıklaşma görülmeye başlandı (36, 41, 42). Fillingham ve Weir (43)" Bütün liderlerin ağırlık merkezlerinin artık organizasyonlarına olan bağlılıktan, vatandaşa ve daha geniş bir nüfusa olan bağlılığa kayması gerektiğini" önermektedir (s.23). Bu, paylaşılan vizyon ve birlikte çözüm üretiminin altını çizen bir niteliktir.

Fillingham ve Weir (43) "Sistem Liderliği" diye bir yaklaşım tanımlıyorlar. Bu yaklaşım iki ayrı ve aynı zamanda birbiriyle alakalı özellik tarafından karakterize edilebilir; i) iş birliği ii) sınırların aşılması – organizasyonel, mesleki ve kişisel böylece liderler olağan sorumluluk ve yetkilerinin sınırlarının ötesine geçebilecekler.

Bireysel Olarak Hemşirelerin ve Diğer Sağlık Profesyonellerinin yapması gerekenler (44-47):

- Sağlığınızı ve iyi olma durumunuzu koruyun
- Zorlukların üstesinden gelebilme yeteneğinizi geliştirmeyi öncelik haline getirin ve iş arkadaşlarınızın da bu özelliklerini geliştirmelerine destek olun
- Bireysel bakımlarını üstlenebilme yeteneklerini geliştirme anlayışına sahip olabilmeleri için hastalar, bakıcılar ve topluluklar aktif şekilde çalışabileceğiniz yollar arayın
- Hizmet kalitesi yüksek hemşirelik uygulamalarının hasta sonuçların üzerindeki pozitif etkisini gösterebilmek için becerilerinizi geliştirin
- Sağlık sistemi üzerine fikir üretme yönteminizi sistem içinde güçlü birliktelikler kurarak geliştirin

Kurumlar/İş verenler

- Sağlık hizmeti çalışanları için Pozitif Çalışma Ortamını sağlayın
- Sağlık hizmeti çalışanlarının sağlık ve refahını destekleyin
- Çalışanlara öğrenme fırsatları sunun
- Kritik vaka değerlendirmesinin organizasyon içinde var olmasını sağlayın
- Afet planlanmalarını yapın

Karar Alıcılar

- Pozitif Çalışma Ortamını sağlayan ve sağlık hizmeti çalışanlarını koruyan yasaları çıkarın ve uygulayın

- Sağlık hizmeti iş gücünü uygun şekilde planlayın ve yönetin. Ulusal düzeyde sağlıkta insan kaynakları planı oluşturun ve etkin şekilde uygulayın
- Hastalık odaklı sistemden önleyici sağlık hizmeti ve sağlıklı olmayı teşvik etme anlayışına geçişi hızlandırın
- Zorlukların üstesinden gelebilme planlamasının sağlık sisteminin stratejik gelişmesinin bir parçası olmasını sağlayın
- Hemşirelik becerilerinin sistem içerisinde optimal kullanımı için hemşirelerin karar alma mekanizmalarında yer almalarını sağlayın

Ulusal Meslek Derneklerinin Rolü

- Mesleklerin katkısını en üst düzeye çıkarmak için ve sağlık profesyonellerinin optimal bir düzeyde çalışabilmesi için kendilerini destekleyen etkin sağlık politikalarının oluşturulmasını sağlayın
- Sistemin her kademesinde sağlık profesyonellerinin katkısının en yüksek düzeyde olması için sağlık alanındaki meslek liderlerini destekleyin

SONUÇ

Sürdürülebilir Kalkınma Hedeflerinde belirtilen amaca ulaşmak için gelecekte yaşanacak zorlukların üstesinden gelebilme kapasitesine sahip, güçlü sağlık sistemleri oluşturmak için birlikte çalışmamız gerektiği açıkça ortadadır.

İhtiyacı olan tüm insanlara kaliteli sağlık hizmetlerini sağlamak hemşirelerin mesleki ve etik bir sorumluluğudur. Adanmış, yenilikçi ve çözüm odaklı profesyoneller olarak hemşireler, çok az durumda olan veya hiç olmayan kaynaklar ve organizasyonel destek ile bile ellerinden her iş gelerek sağlık hizmetini sunmaya devam ediyorlar. Ancak sağlık sistemlerinin zorlukların üstesinden gelebilme kapasitelerini geliştirmek bütün sektörlerin tüm kademelerini içeren şekilde sektörler arası çabayı gerektiriyor. Sağlık hizmetlerinin büyük bir bölümünü hem sağlık sektörü hem de bu sektörün dışındaki meslektaşları ile iş birliği yaparak insanlara ulaştıran hemşireler bu süreçte önemli bir role sahiptir.

Hemşirelerin sağlık sektörü politikalarının reformunda yer alması gerektiğinin başka bir nedeni de bu politikaların hemşirelerin çalışma ortamı üzerinde sahip olduğu büyük etkidir. Sağlık sistemlerinin güçlendirilmesine dair alınan kararlara müdahil olarak, sağlık sistemlerinin gelişmiş bir zorlukların üstesinden gelme kapasitesi ve daha iyi sağlık sonuçları sağlayacak pozitif çalışma ortamlarını oluşturabiliriz.

Hemşireler değişime öncülük etmede tamamlayıcı bir rol oynamalılar. Yeniden yapılandırılmış sağlık sistemleri ve sağlık sistemine dair bütün kararlarda hemşirelerin yer alması ile zorluk zamanlarında bile kaliteli sağlık hizmetini sunabilmek için daha iyi ekipmanlar ile donatılmış olacağız.

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