The definition of pulmonary hypertension (PH) is based on a growing body of evidence and represents the result of ongoing discussions within the PH community over the past 50 years. In 2018, the most recent World Symposium on Pulmonary Hypertension introduced significant changes in the definition of PH by lowering the mean pulmonary arterial pressure threshold to >20 mmHg and (re)introducing the pulmonary vascular resistance ≥3 Wood units (WU) cut-off for all forms of pre-capillary PH. These changes and their potential clinical impact have been the subject of lively discussions in the community and some important questions and controversies have been identified.

In this review we aim to present the development of the definition of PH over the past decades and discuss the main arguments that led to relevant modifications. In addition, we address the practical implications of the most recent changes and controversies that still exist.

Educational aims

- To review the historical development of the definition of pulmonary hypertension.
- To discuss practical implications and current controversies of the currently recommended definitions of pulmonary hypertension and pulmonary arterial hypertension.

According to the proceedings of the sixth World Symposium on Pulmonary Hypertension (WSPH), pulmonary hypertension (PH) is defined by mean pulmonary arterial pressure (mPAP) >20 mmHg. “Pre-capillary PH” is considered if additionally pulmonary arterial wedge pressure (PAWP) is ≤15 mmHg and pulmonary vascular resistance (PVR) is ≥3 Wood units (WU). “Post-capillary PH” is defined as mPAP >20 mmHg with PAWP >15 mmHg. In the case of PVR <3 WU, we talk about “isolated post-capillary PH”, while in the case of PVR ≥3 WU the criteria for “combined pre- and post-capillary PH” are met.
The definition of pulmonary hypertension

Table 1  *Haemodynamic definitions of PH*

| Definition                              | Characteristics          |
|----------------------------------------|--------------------------|
| Pre-capillary PH                       | mPAP > 20 mmHg           |
|                                        | PAWP ≤ 15 mmHg           |
|                                        | PVR ≥ 3 WU               |
| Isolated post-capillary PH             | mPAP > 20 mmHg           |
|                                        | PAWP > 15 mmHg           |
|                                        | PVR < 3 WU               |
| Combined pre- and post-capillary PH    | mPAP > 20 mmHg           |
|                                        | PAWP > 15 mmHg           |
|                                        | PVR ≥ 3 WU               |

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units. Reproduced from [1], with permission from the publisher.

Changes in the definition of PH over time

**WHO meeting on primary pulmonary hypertension: Geneva 1973**

The first World Health Organization (WHO) meeting on PH took place in Geneva, in October 1973. The interest in the topic was raised in previous years due to a sudden increase in the number of PH patients in Switzerland, Germany and Austria, which was associated with the intake of the appetite-reducing drug aminorex. The proceedings of the meeting were published in a 45-page document on primary PH [2]. Although no haemodynamic definition for PH was explicitly provided in this document, the annex contained important statements regarding the diagnosis of PH. Accordingly, 1) right heart catheterisation (RHC) is needed for the reliable measurement of pulmonary pressures, 2) mPAP is little affected by age and does not exceed 20 mmHg in healthy subjects, and 3) PH is definitely present if mPAP exceeds 25 mmHg.

In addition, the range of normal pulmonary capillary pressure was defined as 6–9 mmHg, with an upper limit of normal at 12 mmHg. It should be noted that a wedge pressure measured in a pulmonary artery does not represent the capillary but rather the venous pressure of this vascular segment. The document even addresses changes in pulmonary haemodynamics during exercise by stating that ‘‘for an (cardiac) output of 20 Litres or more, the mPAP does not normally exceed 30 mmHg, and the capillary pressure remains below 20 mmHg. In athletes, for an (cardiac) output of 25 Litres or more, the mean pressure in the pulmonary artery may reach 38 mmHg. ... In older people (61–83 years) the values observed are higher (mPAP up to 50 mmHg), but as in younger subjects the vascular resistance is low’’.

Of note, the document refers to a statement of an earlier WHO Meeting on cor pulmonale that was held in Geneva in 1960 [3]. According to that document, normal mPAP is considered to be ≤15 mmHg and, similar to the 1973 document, PH is diagnosed when mPAP exceeds 25 mmHg at rest. In both documents, the suggested mPAP threshold for PH is largely based on expert opinion, which reflects the wish to define a safety margin above the upper limit of normal mPAP.

**World symposium on primary pulmonary hypertension: Evian 1998**

25 years after the first WHO meeting on PH, in 1998, a second WHO symposium on PH took place in Evian. The main results of the meeting were published in a 27-page document [4]. The term ‘‘pulmonary arterial hypertension’’ (PAH) was introduced as one of five forms of PH and the term ‘‘secondary pulmonary hypertension’’ was abandoned. Interestingly, this document did not explicitly address the haemodynamic definition of PH, implying that the cut-offs of the 1973 WHO meeting were further considered to be valid.

**Third World symposium on pulmonary arterial hypertension: Venice 2003**

The third WSPH took place in Venice in 2003. At that meeting, important changes were implemented regarding the nomenclature, the clinical classification and therapeutic approaches to PH. The previously used term ‘‘primary pulmonary hypertension’’ was replaced by the terms idiopathic and hereditary PAH. It was confirmed that RHC is required to diagnose PH, which was formally defined by mPAP >25 mmHg at rest or >30 mmHg with exercise. In addition, for PAH, further haemodynamic thresholds on PAWP or left ventricular end-diastolic pressure (≤15 mmHg) and PVR (>3 WU) were introduced [5]. Of note, PVR is determined as (mPAP–PAWP)/cardiac output. The basis for the introduction of these parameters and cut-offs is not discussed in detail in the document.

**European Society of Cardiology guidelines on PAH, 2004**

After the publication of the proceedings of the third WSPH, its most important recommendations...
were implemented into the 2004 European Society of Cardiology (ESC) guidelines on PAH [6]. They confirmed that PH was defined by mPAP >25 mmHg at rest or >30 mmHg with exercise. As reference, the document of the first WHO meeting on PH [2] was provided. PAH was haemodynamically defined as mPAP >25 mmHg with PAWP ≤15 mmHg and PVR >3 WU.

Fourth WSPH: Dana Point 2008

The fourth WSPH was held in Dana Point, USA, in 2008, and at this meeting the definition of PH was challenged. A systematic search of the literature including the haemodynamic data of almost 1200 healthy subjects revealed that the upper limit of normal mPAP at rest is 20 mmHg [7]. In fact, this was already postulated at the first WHO meeting on PH in 1973, but now this was broadly accepted due to a large database. This was acknowledged in the proceedings of the fourth WSPH. However, it was decided that the haemodynamic threshold for PH should not be changed to avoid overdiagnosis and overtreatment of patients without significant pulmonary vascular disease [8]. Instead, further investigations were suggested to better determine the prognostic impact of mPAP between 21 and 24 mmHg.

Nevertheless, two changes were proposed for the PH definition. First, instead of mPAP >25 mmHg, from this timepoint, mPAP ≥25 mmHg was considered as the haemodynamic threshold for PH. Second, based on the data on pulmonary haemodynamics during exercise in healthy subjects [7] it was recognised that mPAP during exercise depends on exercise level and on age, and therefore no single mPAP threshold should be used to identify an abnormal haemodynamic response. Therefore, the exercise part of the PH definition was abandoned.

The definition of PAH was not specifically addressed in the proceedings of the fourth WSPH. Although the elimination of the PVR of the previous definition was suggested, this was not discussed in detail in the document.

ESC/ERS PH guidelines 2009

Following the fourth WSPH, the ESC/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH were published in 2009 [9]. In this document, PH was defined as a haemodynamic and pathophysiological state that can be found in multiple clinical conditions, characterised by mPAP ≥25 mmHg.

In these guidelines, two important terms, pre-capillary and post-capillary PH were clearly defined for the first time. Pre-capillary PH was considered in patients with PAWP ≤15 mmHg and normal or reduced cardiac output, while post-capillary PH was considered in those with PAWP >15 mmHg and normal or reduced cardiac output. Post-capillary PH was further divided based on the transpulmonary gradient (TPG=mPAP−PAWP). Patients with TPG ≤12 mmHg were considered to have “passive” post-capillary PH, with the PAWP increase being the main reason for elevated mPAP. By contrast, patients with TPG >12 mmHg were considered as “reactive” (or “out of proportion”) pre-capillary PH, implying that in these patients, the PAWP increase alone does not explain the elevation of mPAP (suggestive of intrinsic changes in the pulmonary circulation adding to the passive increase of mPAP due to an increased PAWP). The theoretical background and the available evidence for the suggested TPG cut-off was not discussed in detail.

PAH was defined as a clinical condition characterised by the presence of pre-capillary PH in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases.

In agreement with the WSPH, the ESC/ERS guidelines abandoned the definition of PH on exercise (mPAP >30 mmHg).

Fifth WSPH: Nice 2013

At the fifth WSPH in Nice in 2013, the haemodynamic definition of PH remained unchanged (mPAP ≥25 mmHg) and due to insufficient available evidence, the re-introduction of an exercise criterion to this definition was not supported [10]. It was also confirmed that the term “PAH” describes a subpopulation of patients with PH that is haemodynamically characterised by the presence of pre-capillary PH.

The definitions of pre-capillary PH and PAH were changed: in addition to PAWP ≤15 mmHg, the PVR >3 WU threshold was re-introduced (previously used for PAH in 2003, but abandoned in 2008). Several advantages were listed in favour of the re-introduction of a PVR criterion for the diagnosis of PAH including: 1) the necessity of performing RHC to assess PVR from its haemodynamic components; 2) the ability to exclude high-flow conditions with normal PVR; and 3) the ability to better differentiate between PAH and PH due to left heart diseases.

Importantly, for the first time, it was discussed that normal PVR at rest is to some extent age-dependent, but PVR >2 WU can be considered elevated in all age groups. Nevertheless, the PVR cut-off value for PAH was kept at 3 WU, because in patients with lower PVR levels, PAH was considered to be unlikely (this was consistent with setting the cut-off for mPAP at 25 mmHg, despite the upper limit of normal being 20 mmHg). In addition, recent US guidelines also used the PVR >3 WU threshold as part of the haemodynamic PAH definition [11]. Beyond the discussions of appropriate haemodynamic thresholds, it was recommended that haemodynamic results are interpreted in their clinical and echocardiographic context with...
regard to the probability of the existence of left heart disease.

The proceedings of the fifth WSPH suggested a change in the nomenclature and definition of post-capillary PH. The term “out-of-proportion” PH was abandoned, and two types of post-capillary PH were introduced based on the level of the diastolic pressure gradient (called “diastolic pressure difference” in this document; DPG = diastolic PAP – PAWP). An “isolated post-capillary PH” was characterised by a PAWP >15 mmHg and DPG <7 mmHg, while a “combined post-capillary PH” was characterised by PAWP >15 mmHg and DPG ≥7 mmHg. The change from TPG to DPG to differentiate between the two types of post-capillary PH was explained by the physiological consideration that diastolic PAP may be less influenced by PAWP than mPAP and that DPG is independent of stroke volume [12, 13]. In addition, out of the PH patients with PAWP >15 mmHg and a TPG >12 mmHg, only those with DPG ≥7 mmHg had evidence for significant pulmonary arterial remodelling and patients in this group had a higher mortality than patients with a DPG <7 mmHg [14].

Two more details were clarified at the fifth WSPH. 1) The use of the terms “pulmonary capillary pressure” or “pulmonary capillary wedge pressure” were discouraged if they refer to a wedge pressure of a pulmonary artery. The only recommended term since this WSPH is “pulmonary artery wedge pressure” (PAWP). 2) The reference for the zero level of the right heart catheter measurements was recommended at the mid-thoracic line in a supine patient halfway between the anterior sternum and the bed surface representing the level of the left atrium [10]. Previously it had been frequently aimed to set the reference at the level of the right atrium.

ESC/ERS PH guidelines 2015

The 2015 ESC/ERS guidelines for the diagnosis and treatment of PH followed the major suggestions of the fifth WSPH. They confirmed once again that PH is defined as an increase in mPAP ≥25 mmHg at rest as assessed by RHC and did not support the use of the term “PH on exercise” [15]. PAH was haemodynamically defined as PAWP ≤15 mmHg and PVR >3 WU. Interestingly, pre-capillary PH was defined as mPAP ≥25 mmHg and PAWP ≤15 mmHg, without including PVR in the definition.

The definition of post-capillary PH remained unchanged (mPAP ≥25 mmHg, PAWP >15 mmHg). However, the definition of the subgroups of post-capillary PH was revised. Now, the use of the term “isolated post-capillary PH” was recommended if the DPG was <7 mmHg and/or PVR <3 WU, while the use of the term “combined post-capillary and pre-capillary PH” was recommended when DPG was ≥7 mmHg and/or PVR >3 WU. By introducing the PVR cut-off in addition to the DPG cut-off to define the different types of post-capillary PH, the authors aimed for consistency with the PAH definition. In addition, in patients with PH and heart failure with reduced ejection fraction, PVR ≥3 WU was associated with increased mortality [16], while the previously described prognostic relevance of DPG could not be reproduced in an independent cohort [17].

Sixth WSPH: Nice 2018

At the sixth WSPH in 2018, again in Nice, the mPAP threshold was lowered from ≥25 mmHg to >20 mmHg [1]. In the proceedings of this WSPH, it was argued that since the first WSPH in 1973, PH had been arbitrarily defined as mPAP ≥25 mmHg. As the upper limit of normal mPAP is 20 mmHg [7], the suggested new definition would no longer be arbitrary, but based on a scientific approach. In addition, recent studies provided evidence that the elevation of mPAP >20 mmHg is associated with a continuous increase of mortality [18, 19] and with an increasing risk for progression of pulmonary vascular disease [20]. However, an abnormal elevation of mPAP alone may not be sufficient to define pulmonary vascular disease as this may be also due to an increase in cardiac output or PAWP. Thus, it was recommended to include PVR ≥3 WU in the definition of all forms of pre-capillary PH (as previously suggested at the fifth WSPH). Pre-capillary PH was defined accordingly by the concomitant presence of mPAP >20 mmHg, PAWP ≤15 mmHg and PVR ≥3 WU, emphasising the need for RHC with mandatory measurement of cardiac output and accurate measurement of PAWP (figure 1). After careful consideration of the changes in the general definition of PH, the haemodynamic definitions of post-capillary PH were also adapted and included only mPAP, PAWP and PVR. The term “isolated post-capillary PH” has been suggested for the haemodynamic condition with mPAP >20 mmHg, PAWP >15 mmHg and PVR <3 WU, while “combined pre- and post-capillary PH” is considered if three conditions are met: mPAP >20 mmHg, PAWP >15 mmHg and PVR ≥3 WU. As recent data revealed that besides PVR, DPG, TPG and pulmonary arterial compliance are also associated with survival in patients with PH and left heart disease [21, 22], beyond a strict haemodynamic definition, the proceedings suggested to also take these haemodynamic markers into consideration to better determine the prognosis of patients.

Although important novel data on pulmonary haemodynamics during exercise had been published in the years before the sixth WSPH [23, 24], some uncertainties persisted especially concerning normal haemodynamic changes with ageing, as well as the prognostic and the differential diagnostic relevance of exercise haemodynamics. Therefore, the re-introduction of a clinically useful definition for exercise PH was not possible.

The major changes in the haemodynamic definitions of PH and PAH over the past 50 years are outlined in table 2.
The definition of pulmonary hypertension

Practical implications of current changes

The most recent WSPH, in 2018, introduced significant changes in the definition of PH by lowering the mPAP threshold to >20 mmHg and (re-)introducing the PVR ≥3 WU threshold for all forms of pre-capillary PH. These changes and their potential clinical impact have been the subject of lively discussion in the community. Recent data suggest that the number of new patients with pre-capillary PH remains limited, because the majority of patients with mPAP 21–24 mmHg have PVR <3 WU and therefore do not fulfil the proposed criteria for pre-capillary PH [25–27]. A more detailed analysis of a large single-centre cohort of patients undergoing RHC revealed that the new criteria for “pre-capillary PH” will be met by the same number of patients as the old criteria. However, some of the patients are re-grouped. There is a group of patients with mPAP 21–24 mmHg and PVR ≥3 WU who are now considered to have pre-capillary PH, while the same number of patients with mPAP ≥25 mmHg but PVR <3 WU are not considered to have pre-capillary PH anymore [28]. By comparing both groups, patients with mPAP 21–24 mmHg and PVR ≥3 WU appear to have lower mPAP and PAWP, lower 6 min walk distance and diffusion capacity for carbon monoxide, but higher PVR as compared with patients with mPAP ≥25 mmHg but PVR <3 WU. In addition, isolated pulmonary vascular disease appears as the main reason behind elevated mPAP and PVR in patients with mPAP 21–24 mmHg and PVR ≥3 WU and this group appears to have a poorer prognosis. Therefore, the haemodynamic and clinical profiles of “new pre-capillary PH” patients correspond more to the aims of the sixth WSPH to recognise patients with early forms of pulmonary vascular disease and poor prognosis.

Current controversies of the PH definition

There are some important questions and controversies regarding the currently suggested PH definition that have been addressed at recent WSPH meetings and which remain areas of discussion [29].

First, the necessity for lowering of the mPAP threshold to >20 mmHg may be questioned. Most frequently the concern of overdiagnosis and overtreatment of PH has been expressed in this regard. This issue was addressed in the proceedings of the sixth WSPH with the argument that the main cause of overdiagnosis and treatment of pre-capillary PH may probably be the failure to confirm the diagnosis by RHC. The concern of overdiagnosis may be attenuated by recent studies, showing that the number of newly diagnosed patients with pre-capillary PH is relatively low [26–28] and many of them may indeed suffer from early pulmonary vascular disease. It is important to emphasise, however, that changes in the haemodynamic definition of PH do not influence the indication for...
The definition of pulmonary hypertension

PAH therapy. The evidence for the beneficial effects of PAH therapies is exclusively based on therapeutic trials with PAH patients (or non-operable chronic thromboembolic PH) with mPAP ≥25 mmHg.

Second, the optimal threshold of PAWP to define pre-capillary PH may be challenged. Although the upper limit of normal PAWP is frequently considered to be 12 mmHg [30], the proceedings of the sixth WSPH suggested that the PAWP ≤15 mmHg threshold is maintained for the identification of pre-capillary PH [1, 31]. However, it has also been recommended that in patients with PAWP between 13 and 15 mmHg the probability of heart failure with preserved ejection fraction should be assessed and the performance of provocative testing (i.e. fluid loading or exercise) may be considered in order to uncover significant left heart disease.

Third, in the proceedings of the fifth and the sixth WSPH, it has been mentioned that the upper limit of normal PVR is at 2 WU, but in both documents the use of the PVR ≥3 WU threshold was suggested for the definition of pre-capillary PH and this threshold was also used to define PAH by the 2015 ESC/ERS PH guidelines [15]. In the proceedings of the sixth WSPH it has been acknowledged that the use of a cut-off value of PVR ≥3 WU is conservative and it has been argued that the value of PVR ≥3 WU may be considered clinically relevant in different clinical situations, suggesting the presence of a significant pulmonary vascular disease, e.g. it has been recommended as the threshold value above which the correction of congenital systemic-to-pulmonary shunts becomes questionable [1].

Finally, the proceedings of the sixth WSPH extensively discuss the question of whether exercise PH should be re-introduced as part of the PH definition. Although the potential benefits of such a definition have been recognised (i.e. to detect pulmonary vascular disease at an earlier stage) important limitations have been highlighted that should be addressed, before a clinically useful definition of exercise PH can be re-introduced.

Table 2 Changes in the haemodynamic definitions of PH

| WSPH/guideline document | PH | PAH | Pre-capillary PH | Post-capillary PH | Exercise PH |
|--------------------------|----|-----|------------------|-------------------|------------|
| First WSPH (Geneva 1973) | mPAP >25 mmHg | Not defined | Not defined | Not defined | mPAP >30 mmHg |
| Second WSPH (Evian 1998) | No change | No change | No change | No change | No change |
| Third WSPH (Venice 2003) | No change | mPAP >25 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU | No change | No change | No change |
| ESC PAH Guidelines 2004 [6] | No change | No change | No change | No change | No change |
| Fourth WSPH (Dana Point 2008) | mPAP ≥25 mmHg | mPAP ≥25 mmHg + PAWP ≤15 mmHg | No change | No change | Not defined |
| ESC/ERS PH Guidelines 2009 [9] | No change | No change | mPAP ≥25 mmHg + PAWP ≤15 mmHg | mPAP ≥25 mmHg + PAWP >15 mmHg (passive: TPG ≤12 mmHg, reactive: TPG >12 mmHg) | No change |
| Fifth WSPH (Nice 2013) | No change | mPAP ≥25 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU | mPAP ≥25 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU | mPAP ≥25 mmHg + PAWP >15 mmHg (isolated: DPG <7 mmHg, combined: DPG ≥7 mmHg) | No change |
| ESC/ERS PH Guidelines 2015 [15] | No change | No change | mPAP ≥25 mmHg + PAWP ≤15 mmHg | mPAP ≥25 mmHg + PAWP >15 mmHg (isolated: DPG <7 mmHg and/or PVR ≥3 WU, combined: DPG ≥7 mmHg and/or PVR >3 WU) | No change |
| Sixth WSPH (Nice 2018) | mPAP >20 mmHg | mPAP ≥20 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU | mPAP ≥20 mmHg + PAWP ≤15 mmHg + PVR ≥3 WU | mPAP >20 mmHg + PAWP >15 mmHg (isolated: PVR <3 WU, combined: PVR ≥3 WU) | No change |
Self-evaluation questions

1. A patient presents with the following pulmonary haemodynamics: mPAP: 45 mmHg, PAWP: 8 mmHg, PVR: 12 WU. Based on the proceedings of the most recent WSPH, which of the following haemodynamic terms fits for this patient?
   a) Pre-capillary PH
   b) Isolated post-capillary PH
   c) Combined pre- and post-capillary PH
   d) None of the above, the patient has no PH

2. A patient presents with the following pulmonary haemodynamics: mPAP: 24 mmHg, PAWP: 8 mmHg, PVR: 3.5 WU. During exercise, mPAP increases to 35 mmHg. Based on the proceedings of the most recent WSPH, which of the following statements is true?
   a) The patient has PAH and medical therapy is indicated for this condition
   b) The patient fulfils the criteria of pre-capillary PH
   c) The patient has PH based on his elevated mPAP during exercise
   d) The patient fulfils the criteria of isolated post-capillary PH

3. Which zero reference level should be used for haemodynamic measurements during RHC in the supine position?
   a) Anterior axillary level
   b) 1/3 thoracic level
   c) Mid-thoracic level
   d) 10 cm above table level

4. How will PVR be calculated?
   a) Stroke volume divided by pulmonary arterial pulse pressure
   b) Mean pulmonary arterial pressure divided by cardiac index
   c) Transpulmonary gradient divided by cardiac output
   d) Peak oxygen uptake divided by heart rate

Conclusion

In conclusion, the definition of PH and PAH underwent several changes during the past 50 years representing the growing body of evidence and the ongoing discussions within the PH community. There has been an increasing effort to provide evidence-based haemodynamic thresholds reflecting the upper limit of normal values, their prognostic relevance and practical considerations. With the appropriate clinical context, such haemodynamic thresholds represent the cornerstone of PH diagnosis and have been providing a basis for the design of clinical trials and for decision making in daily patient care.

Key points

- PH is currently defined by mPAP >20 mmHg.
- “Pre-capillary pulmonary hypertension” is considered, if mPAP is >20 mmHg, PAWP is ≤15 mmHg and PVR is ≥3 WU.
- “Post-capillary pulmonary hypertension” is defined as mPAP >20 mmHg with PAWP >15 mmHg. In the case of PVR <3 WU, we talk about “isolated post-capillary pulmonary hypertension”, while in the case of PVR ≥3 WU the criteria for “combined pre- and post-capillary pulmonary hypertension” are fulfilled.
- Exercise PH is currently not part of the haemodynamic definition of PH.
- The evidence for the beneficial effects of PAH therapies is exclusively based on therapeutic trials with PAH patients (or non-operable chronic thromboembolic PH) with mPAP ≥25 mmHg.
The definition of pulmonary hypertension

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Conflict of interest

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Suggested answers

1. a
2. b
3. c
4. c

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